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NEURAL ORGANIZATION IN THE PRIMATE RETINA

R. J. MacGregor

PREPARED FOR:
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The RAND Corporation
SANTA MONICA • CALIFORNIA

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PREFACE

This study is part of an investigation conducted for the Advanced Research Projects Agency. The following publications represent several phases of this investigation: RM-5015-ARPA, A Display Simulator for Colored-Image Presentation; RM-4196-ARPA, A Critical Review of the Experimental Foundation of Human Color Perception; and RM-4770-ARPA, Temporal Factors in Subjective Color. The present study, which addresses the neural mechanisms of visual perception, constitutes part of a phase of this investigation, of which the following studies are components: RM-4870-ARPA, A Digital-Computer Model of Spike Elicitation by Postsynaptic Potentials in Single Nerve Cells; and RM-4877-ARPA, Pulse Trains in Lateral Geniculate and Retinal Ganglion Nerve Cells.

Although the program is concerned with human vision, the lack of adequate neuroelectric data taken from humans has compelled us to utilize nonhuman data pertaining to the neural processes of vision. Nonetheless, several lines of evidence suggest that neural processes in the retina are comparable for most vertebrates. Thus the evidence described in the present report bears directly on problems of human vision.

SUMMARY

This study surveys the neurohistological, neuroelectrical, and neurophysiological evidence relating to neural organization in the primate retina and applies this information to the understanding of retinal organization.

Histological studies suggest a primary classification of neural elements into five main types. There is a very wide variety of subclasses of the main types, but also indications of systematic subclassification. A fundamental characteristic of retinal organization is the occurrence of extensive cross-connections and a consequent overlap of functional pathways. Polyak has presented a relatively complete description of retinal patterns of interconnection, but his pronouncements have not always been corroborated by recent electronmicroscopic investigations.

A salient feature of neuroelectric activity recorded from ganglion cells is the organization exhibited by the receptive field of core and opposing periphery regions. Firing frequency in ganglion cells exhibits a logarithmic-like dependence on stimulus intensity. S-potentials, on the other hand, show that electrical activity distal to bipolar cells is graded rather than pulsatile. The amplitudes of S-potentials depend on stimulus intensity approximately as $I/(1 + I)$. Their spectral properties have helped provide resolution of the apparent conflict between three-color and opponent-process theories of color vision.

The rudiments of transfer mechanisms between single nerve cells and their properties are discussed. Pertinent modes of transfer are excitatory synaptic, inhibitory synaptic, presynaptic inhibition, electrotonic junctions, and field influence.

Retinal organization is discussed in terms of neurohistological, electrical, and physiological concepts. Outstanding problems include adaptation and receptor interaction, spontaneous activity, efferent influence, and amacrine function. At present, all modes of behavior and interneuronal transfer in the retina must be found by inference, and the mechanisms underlying these processes are particularly obscure.

A hypothetical theoretical framework for an initial consideration of retinal organization is presented. This framework is based upon a modification of Polyak's classification and interconnection patterns, and upon a hypothetical specification of the physiological modes of transfer at interneuronal junctions.

A generator theory that attempts to account for the properties of S-potentials in and distal to bipolar cells is presented. On the basis of this theory, an attempt is made to interpret in part the encoding of stimulus intensity.

The concluding section presents several orientations from which the work may be viewed and indicates directions in which future work might profitably proceed.

SYMBOLS

E = transmembrane potential

I = stimulus intensity

A = total area of retina

r = radius of eyeball

θ, φ = angular coordinates in spherical system with origin at center of eyeball

E^* = equilibrium potential of synaptic process

CONTENTS

I. INTRODUCTION

This work is part of a program which attempts to apply the methods of the engineering sciences to attain a quantitative understanding of some aspects of retinal function. Neurophysiological mechanisms are applied to retinal interconnection patterns to help understand retinal neuroelectric data and, in turn, some aspects of their relation to visual perception. A marked conceptual distinction is drawn between neuroelectric data (wherein one speaks of the properties of spike trains, "off" and "on" responses, receptive-field organization, properties of the ERG, S-potentials, etc.) and neurophysiological mechanisms (wherein one considers the characteristics and properties of synaptic activation, the propagation and interaction of potentials on neural membranes, etc.). The former are properties of the system that we hope to understand, but the latter are the tools that, in the final analysis, will provide the basis of our understanding. The methods of the engineering sciences may be of some value in this task, which is shared by many investigators with diverse backgrounds and orientations.

The retina is a promising point of entry for investigations of neural mechanisms subserving visual perception, as a large body of neuroelectric data has been obtained from retinal elements.[1] Retinal networks seem to constitute meaningful functional units, as their activity depends but little on higher neural structures. Certain fundamental and well-documented features of visual perception seem to reflect properties of the retinal networks. For example, the relation of subjective sensation to stimulus intensity, the ability to discriminate the flashes of a flickering stimulus, and the effect on subjective sensation of spatial or temporal contrast in stimulation, all have striking counterparts in retinal electrical behavior.[1] The ability to discriminate the spectral composition of stimuli also originates in the retina.

The foregoing program is both attractive from the standpoint of theory and extremely challenging. Histological, neuroelectrical, and neurophysiological data are all germane to this task; each of these fields contains many diverse, complicated, and often contradictory

features, is incompletely understood today, and is rapidly increasing in content. Furthermore, it is by no means clear what analytical tools may be most appropriate to a meaningful analysis, assessment, and description of the behavior of collections of nerve cells. Perhaps computer simulation, or some succinct and meaningful form of statistical mechanics, will prove to be the only realistic approach.

In any case, a fundamental obstacle to the assessment of retinal function is that retinal histology has not provided a clearly defined set or sets of interconnected elements for analysis. There is ignorance about meaningful subclassifications of cell types, about interconnection patterns and their functional significance, and indeed, about whether certain cell types are neural elements.

These fundamental questions remain unanswered even though neural elements of the retina have been the focus of histological study for about a century. Several factors have contributed to this state. First, the situation is indeed complicated. The retina contains some 40 or 50 million nerve cells of several classes and subclasses, most of which branch profusely and interconnect diffusely. Second, until about the last decade retinal studies were performed with the light microscope, whose resolution has not proved capable of unraveling the diffuse and intricate patterns of interconnection. Third, the retina contains two classes of cells - amacrines and horizontals - that have remained singularly enigmatic. The amacrine cells exhibit an anomalous pattern of ramifying dendritic branches and often appear to have no axons; consequently, there is no clear functional polarization of this cell type. The horizontal cells cannot be classified as nerve cells on the basis of histology alone. Furthermore, both types of cells make extensive and diffuse lateral connections within the retina, greatly complicating the overall patterns of interconnection. Fourth, neuroelectric technology has only in recent years approached the state where its findings may substantially promote the understanding of retinal organization. And fifth, only in recent years has the study of neurophysiological mechanisms provided indications of the significance of various histological characteristics.

Thus, we recommend a highly skeptical attitude to any and all theoretical or interpretative passages in the existing literature. (This caveat applies equally to the discussion presented in Sections IV and V below.)

Nonetheless, reliable knowledge about retinal organization has accumulated rapidly in recent years. The advent of the electron microscope in itself ensures that the detailed delineation of interconnection patterns is only a matter of time and diligence. This, together with accomplished and projected advances in neurophysiology and in neuroelectric technology and data accumulation, suggests an optimistic prognosis for the future understanding of retinal function.

Many current texts and volumes dealing with the present subject matter within a broader context contain superficial treatments of retinal neurohistology. However, this writer is not aware of any adequate assessment of the subject matter.

The present Memorandum contains both highly speculative and (it is hoped) objective sections. Its primary purpose is to provide an overview of neural organization in the retina. Section II presents a documented review of retinal neurohistology, comprising cell classification schemes, interconnection patterns, and densities and distributions. Section III discusses rudiments of neuroelectrical and neurophysiological information that are germane to retinal organization.

Section IV presents a discussion of retinal organization, highlighting salient interpretive difficulties and outlining a tentative and hypothetical scheme of organization.

Section V addresses neurophysiological processes of the outer plexiform layer, and attempts to show that the properties of retinal S-potentials and the rudiments of subjective-intensity encoding may be understood on the basis of an appropriate application of the generator theory of nerve cell function.

Section VI contains concluding remarks.

II. NEURAL ELEMENTS OF THE RETINA

This section presents a review of retinal neurohistological studies of vertebrates. The discussion is not restricted to findings from primates, since the basic characteristics of retinal neural organization are common to most vertebrate species.

The functional characteristics of a given neural system are determined both by the properties of the individual elements and by their patterns of interconnection. Thus, in this section we consider histological studies relating to classification and subclassification of retinal nerve cells, their densities and distributions, and their patterns of interconnection. However, primate studies, and human studies in particular, are emphasized. Our data include early work performed with the light microscope (most notably by Dogiel,[2] Cajal,[3] and Polyak[4]) as well as more recent studies with the electron microscope. The section concludes with a summary of the salient findings.

Figure 1 illustrates the topography of the retina and its position within the eyeball.

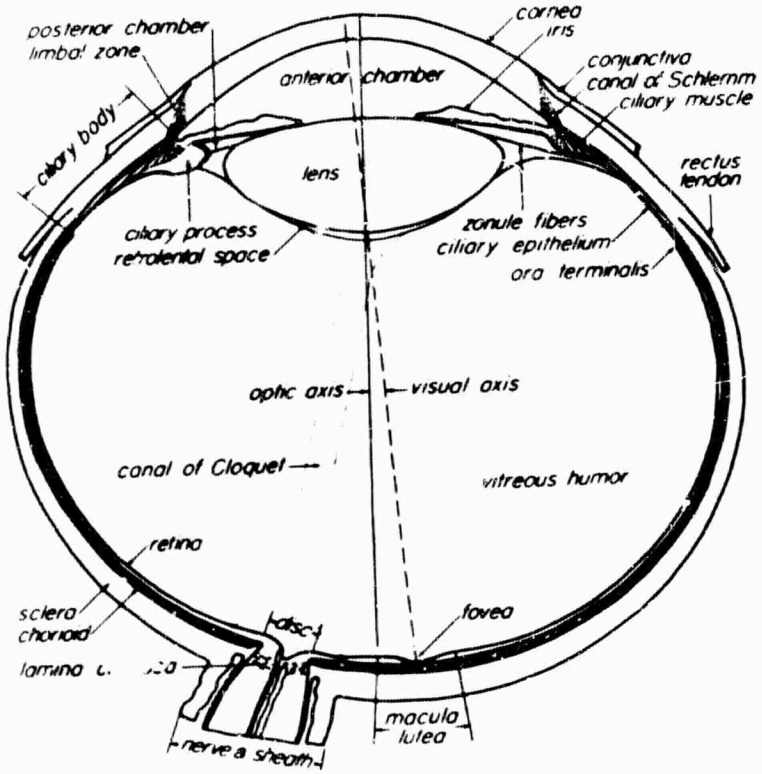
A. CLASSIFICATION OF CELLS

As illustrated in Fig. 2, retinal nerve cells can be classified into five main groups on the basis of location, orientation, and gross morphological characteristics.

Receptors are located in the outermost layer of the retina (receptor layer) and are oriented vertically, extending from the layer of pigment into the outer plexiform layer. They are approximately 2 microns in diameter and about 60 to 70 microns long.

Horizontal cell bodies are found in the external extremities of the inner nuclear layer. These cells, which range from about 8 to about 80 microns in diameter, are oriented laterally, and their processes may extend over areas exceeding a millimeter in diameter.

Bipolar cells are found in the inner nuclear layer. About 5 to 10 microns in diameter, their cell bodies are oriented vertically, sending into the outer plexiform layer a single dendritic stem which ramifies near the internal receptor endings and sending an axonal process



Optic Nerve Fibers

Ganglion Cell Layer

Inner Plexiform Layer

Inner Nuclear Layer

Outer Plexiform Layer

Outer Nuclear Layer

Receptor Layer

Fig. 1 -- Horizontal section and retinal stratification of the primate eye[5] (by permission from G. L. Walls, The Vertebrate Eye and its Adaptive Radiation, Hafner Publishing Co., New York, 1957).

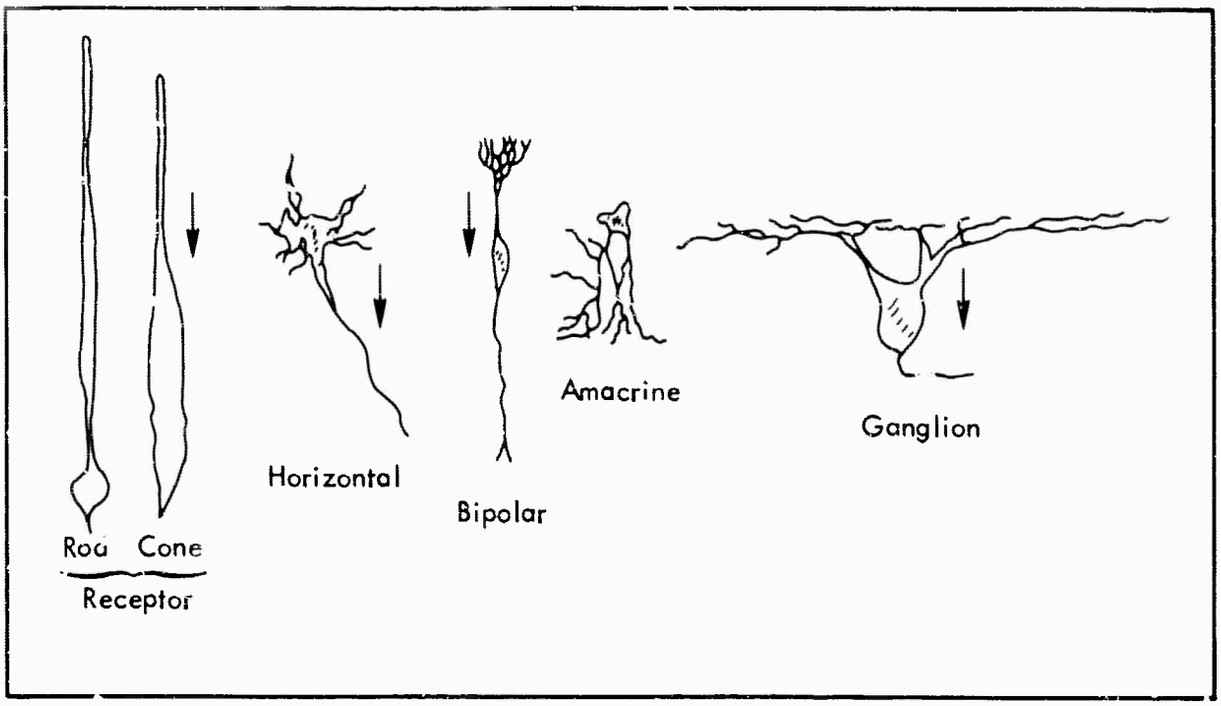


Fig. 2 -- Five main classes of retinal neural elements.[4,5]

into the inner plexiform layer. Their dendritic arborization may extend over an area of the order of 50 microns in diameter.

Amacrine cells are found near the internal extremeties of the inner nuclear layer. Their cell bodies are approximately 10 microns in diameter, and appear to be laterally oriented. Amacrines send dendritic processes into the inner plexiform layer, where they ramify and spread laterally over an area of the order of about 100 to 300 microns in diameter. These cells are characterized by the absence of an axonal process.

Ganglion cells form the innermost layer of cells in the retina, having cell bodies about 20 microns in diameter. Their dendrites extend into the inner plexiform layer, where the branching patterns may extend laterally over an area from 8 to about 600 microns in diameter. Their axons run laterally across the retina to exit at the optic disc, and from there proceed in a central direction to form the optic nerve.

Not so readily apparent histologically, but probably equally important with respect to retinal function, are the subgroups within each classification. A definitive subclassification of retinal nerve cells will not be possible until the cell types are related to retinal function. Such a classification cannot be based upon morphology and interconnections alone, nor upon direct correlations between morphological features and observed electrical behavior. It should reflect the role of those neurophysiological mechanisms emphasized by a cell through its morphology and patterns of interconnection. Section III discusses the cellular dimensions upon which such a functionally meaningful subclassification might be based.

There are no obvious histological criteria for subclassification, and different investigators have suggested different schemata. The following paragraphs describe for each major type of cell the subdivisions suggested by histological studies. Most of the subtypes discussed are illustrated in Fig. 3.

Receptors

Histological investigations have distinguished only two types of receptors: rods and cones.[6-9] Photochemical,[10-12] electrical,[13-15] and behavioral[16] evidence supports this dichotomy, and also suggests a subdivision of cones into three types on the basis of their spectral sensitivity.* However, histological studies have not indicated a subclassification of cones.

Horizontal Cells

Cajal[3] defined two groups of horizontal cells on the basis of their location. The group found at the inner extremity of the outer plexiform layer he called "external," and those immediately internal to these, "internal." He describes the external horizontals as resembling a star; they are multipolar and extend dendritic processes laterally in all directions. The dendritic stems branch often and terminate

*See Ref. 17 for a critical review relating to cone subdivision based on spectral characteristics.

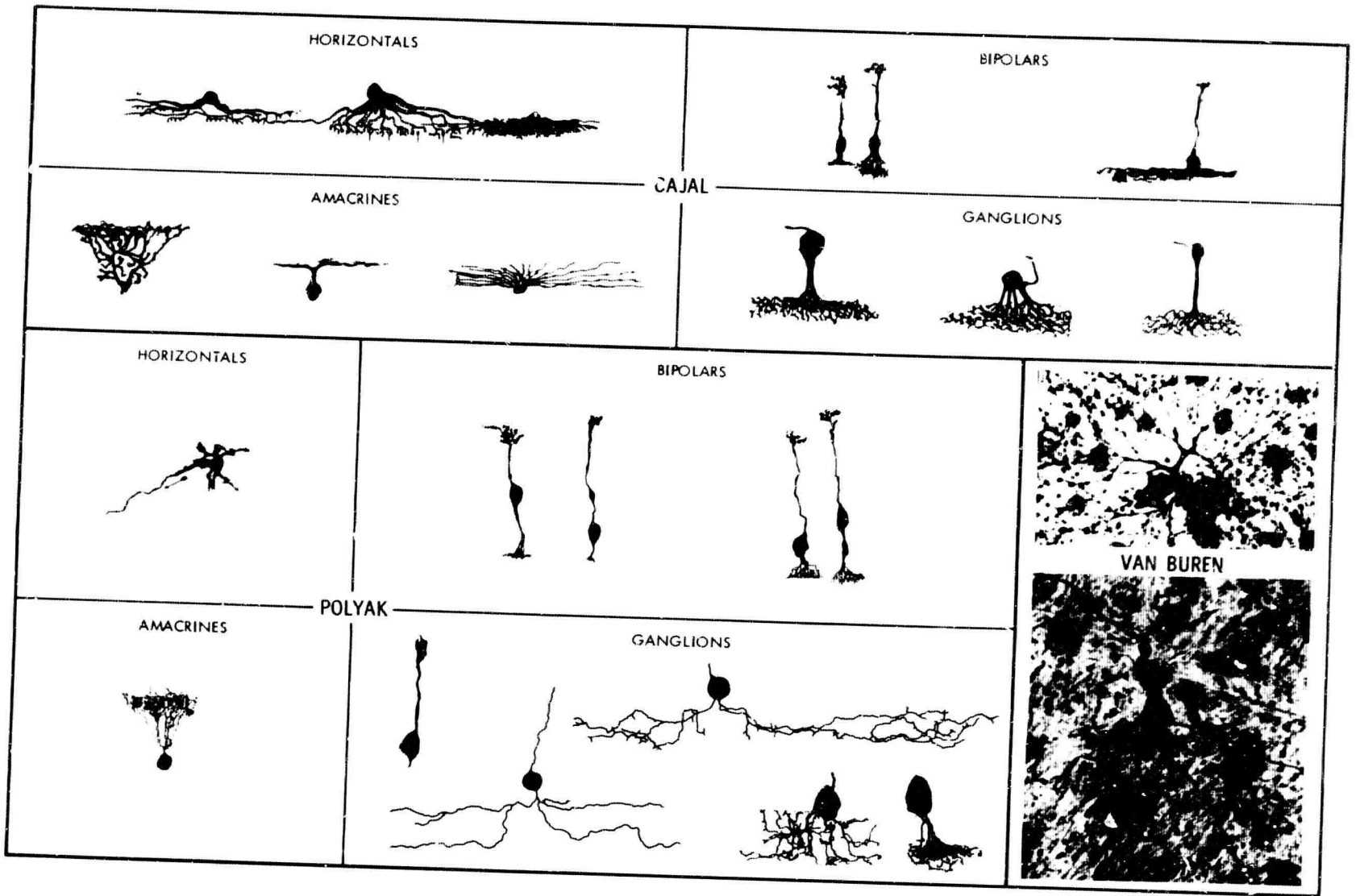


Fig. 3 -- Suggested subclasses of retinal neural elements.

under the feet of cones, with which they seem to form a "special connection." Cajal found it difficult to follow the axons of these cells, which seem to describe a variable horizontal trajectory and terminate in an arborization in the outer plexiform layer, sometimes sending off collaterals that also arborize.

The internal horizontals are somewhat larger than the external. They exhibit a number of short, thick dendritic stems that arborize and terminate at the external extremity of the outer plexiform layer. Cajal defines two subclasses of internal horizontals on the basis of their axons. Cells of the first exhibit large axons that traverse the outer plexiform layer inwardly a short distance before sending out ramifications in lateral directions. Cells of the second subclass have a very large axon that traverses a variable lateral path, often quite long, and terminates in an extensive, complicated, and elegant arborizaton. On the varicose branches of these terminations are "appendices" that penetrate the feet of rods. These axons also sometimes exhibit collaterals that arborize.

Polyak,[4] on the other hand, does not acknowledge a subclassification of horizontal cells, which he describes as resembling octopi. According to Polyak, these cells have several short, thick dendritic stems spreading in all lateral directions, each of which divides into a half-dozen or so terminal branches that carry minute spherical varicosities at their ends. The branchlets and varicosities are assembled into a set of cups or baskets which fit the vitreal face of cone pedicles. The axon extends laterally over several hundred microns and then branches repeatedly, forming a dense arborizaton that covers an area much larger than the dendritic spread of the cell.

Gallego[18] claims that Polyak has described only the internal horizontals described by Cajal, and has overlooked the external variety. He claims further to have seen very clearly a layer of external horizontal cells.

Gallego describes a class of horizontals which he believes comprises small members of Cajal's external variety. These have three of four large dendritic stems that extend laterally in all directions and branch repeatedly. Gallego finds that these cells seem to exhibit no axons;

he attempts to reconcile this feature with Cajal's work by claiming that Cajal's earl y description[19] of external horizontals is ambiguous, and in particular that his descr.ption of their axons is really applicable only to large external horizontals. This resolution cannot be accepted, however, as Cajla's later description[3] of external horizontals fails to acknowledge a meaningful division between large and small varieties, but contains the explicit description of axons on external horizontals summarized above.

De Testa[20] suggests, on the basis of their location, that there are three classes of horizontal cells in the teleost retina. All these types are quite similar to those described by Gallego. De Testa also noted that these horizontals exhibited no axon-like prolongation.

Although the interspecific similarity of retinal organization has been often emphasized,[5,8,9,21] several investigators have recently suggested that the horizontal cells might vary phylogenetically. Villegas has observed that the horizontal cells of fish seem to be glia, whereas primate horizontal cells seem to be neurons.[8,9,21] Gallego[18] has suggested that the horizontal cells of the cat should be regarded as a type of intermediate nervous element pos essing characteristics of both neuroglia and neurons.

On the other hand, Svaetichin[22] and De Testa[20] have suggested that horizontal cells should be regarded as a third class of nervous tissue, which they call "controller cells."

Missotin[23] has found in external horizontal cells of the human a group of organelles not typically present in neural elements. These organelles prove to be associated with particles of ribonucleoproteins. On the basis of this observation, Missotin suggests that external horizontal cells might be the source of a particularly intense nervous activity. Previous studies had revealed these organelles only in the external horizontal cells of the human and the chimpanzee; Missotin found the organelles in the human only in the extramacular region.

Bipolar Cells

Cajal[3] has contended that bipolar cells connect exclusively with either rods or cones, and he defines two classes of bipolar cells on

this basis. He describes the cone bipolar as ovoid and small, with a thick dendritic stem that arborizes at the interior stage of the external plexiform layer into long horizontal branches that contact the feet and filaments of several cones. The axon of this cell is thin and ramifies at one stage of the internal plexiform layer into a short, flat, varicose arborization.

Cajal also found members of this class that differed slightly from the foregoing description. These cells, which he called "giant bipolars," had large cell bodies adjacent to the outer plexiform layer and exhibited horizontal arborizations with very extended and numerous branches.

The rod bipolar he describes as larger than the cone bipolar. It exhibits two or three short, thick dendritic stems, each of which ramifies into an "elegant bouquet" of short, thin branches in the outer plexiform layer; its axon is rather thick and traverses the entirety of the inner plexiform layer, where it ramifies into a simple arborization of short and thick branches which articulate with both the soma and dendrites of ganglion cells.

Polyak,[4] on the other hand, disputes Cajal's contention that bipolar cells connect exclusively with rods or cones. He proposes that bipolars be grouped as polysynaptic and monosynaptic. The former group connects with both rods and cones, whereas the latter connects only with cones. The polysynaptic group he further divides into three classes: the mop, the brush, and the flattop. The monosynaptic group contains a single class, the midget.

The mop bipolar exhibits a relatively thick dendritic stem that divides repeatedly in the inner zone of the outer plexiform layer, forming a small "mop" of delicate, filamentous terminal branches. Its axon, which is usually much thinner than the dendritic stem and is provided with spindle-shaped varicosities, traverses the inner plexiform layer, and divides at its inner extremity into two or three thick swollen branches that terminate in crude, irregularly spherical varicosities.

The brush and flattop bipolars both exhibit a single primary dendritic stem that may be slender or fairly stout and extends into the outer plexiform layer where it ramifies. The character of the dendritic

arborization is the basis for Polyak's distinction between brush and flattop varieties: "The dendritic ramifications of one type [he writes] resemble a brush with the tips of its thin bristle-like filaments cut off straight. The other type has undulating branches which sweep laterally."[4] Both types exhibit relatively thin axons which ramify exclusively in the outer layers of the inner plexiform layer. The arborizations are more delicate than those of the mops, and consist of a "small clump of thin, short twigs, swollen in places into varicosities and with minute buttons at the ends, occasionally all twisted into a fine meshwork."

Polyak characterizes the midget bipolar as the most conspicuous bipolar cell of the human and simian retina. Its cell body is small; its dendritic stem is short and thin, and passes directly to the outer plexiform layer where it ramifies; its dendritic arborization consists of about a dozen thin and very short branchlets which remain very close together, and in general all make contact with a single cone. The axon is thin and terminates with a few lumpy swellings in two tiers in the inner plexiform layer.

In addition to these main classes of bipolars, Polyak describes a "centrifugal bipolar" whose morphological features seem to suggest an internal-to-external polarity. The cell body is found in the inner nuclear layer. A relatively thin process extends externally and divides into a few short branches; a terminal arborization is produced by further subdivision of these branches into fine twigs. Polayk suggests that this tree resembles an axon and its terminating ramifications rather than a dendritic pattern. One or more processes extend vertically inward and branch repeatedly, producing a cluster that spreads in the inner plexiform layer.

Villegas, reporting recent work with the electron microscope, makes the following remarks pertinent to bipolar classification:

> In the monkey, three nuclear types are seen in the bipolar cell layer. The first type comprises large grouped granules forming dense zones irregularly arranged, in contrast with less dense granular portions. The second type, with a pale appearance, has small granules homogeneously distributed. The third type of nuclei also presents a regular

> distribution of granules but its density is greater than that of the second type.[21]

In a subsequent electronmicroscopic examination of the human retina, Villegas,[8] although noting a "striking similarity between the structure and organization of the human retina and the other vertebrate retinae, especially that of the monkey," makes no comment regarding this classification of bipolar cells.

Brown and Major[24] define two classes of bipolar cells in the cat retina. The first corresponds to Cajal's "cone bipolars," and the second to Cajal's "rod bipolar" or Polyak's "mop bipolar."

Amacrine Cells

Cajal[3] described four classes of amacrine cells: unistratified, bistratified, diffuse, and displaced.

The unistratified type is characterized by a dendritic arborization that lies in a single lateral plane in the inner plexiform layer. Most commonly, the dendritic tree is connected to the cell body by a single trunk. Cajal described four subclasses of this variety on the basis of dendrite size and branching pattern. The cells of the most common subclass exhibit a single thick trunk that descends from the cell body into the internal plexiform layer, where it ramifies into a lateral arborization. This subclass may be further subdivided on the basis of the level in the inner plexiform layer where the arborization occurs. A second subclass is very similar to the first, but exhibits a very thin descending trunk and very fine, very long dendrites. A third variety comprises cells whose trunk and trunk branches are very thick and very long. A final subclass exhibits a varicose dendritic arborization.

Cajal only rarely saw bistratified amacrines. These exhibited a single descending trunk that branched rather extensively into both the inner and outer extremities of the inner plexiform layer.

The diffuse amacrine cell exhibits dendritic branchings that ramify throughout the inner plexiform layer. Cajal observed that this cell is abundantly represented and described two subclasses. The first subclass exhibits two or three medium-sized primary stems that spread

obliquely through the inner plexiform layer. These stems branch repeatedly, and the secondary branchings are extremely varicose. These varicose branchings spread through the entire inner plexiform layer, but the longest stems provide a dense horizontal plexus in the innermost layer of the inner plexiform layer. A second subclass exhibits a short, thick trunk that branches very close to the cell body and a varicose arborization that is composed of relatively thick subbranches which extend through the inner plexiform layer. In general, the arborizations of this subclass cover a smaller volume than those of the first.

Cajal labeled his fourth class "displaced," as the cell bodies were found in the inner plexiform layer, slightly internal to the other varieties. The cells exhibited long and ramified dendritic expansions which were sometimes confined to the lateral plane containing the cell body, but sometimes spread throughout the inner plexiform layer.

Polyak[4] gives the following description of amacrine cells:

> The amacrine cell body is in the lowermost zone of the inner nuclear layer. From it one or several main processes descend, which by repeated subdivision produce an 'arborization' spreading in the inner plexiform layer.
>
> The arborization is loose, composed of a few long, thin, smooth branches dividing but little, with only a few spindle-shaped varicosities and with terminal spherical and globular swellings. In the other amacrine cells, on the contrary, the arborization is dense, compact, made up of many branches and twigs carrying numerous swellings, buttons, spines, and varicosities of various shapes. The arborization, especially if large, spreads over the entire thickness of the inner plexiform layer, its lowermost twigs touching the bodies of the ganglion cells. In smaller amacrines the arborization, usually at the end of a single descending process, is small and spreads in only one or two of the several zones of the inner plexiform layer.
>
> According to the appearance, size, and area in which the arborizations spread, several varieties of amacrine cells may be distinguished. Future investigation will show whether there is a morphological and functional basis for such subdivisions...

Polyak also suggested that some amacrines may have axons which spread horizontally in the inner plexiform layer. He based this suggestion on his observation of fibers in the inner plexiform layer which appeared to have the character of axons.

Amacrine cells also appear to have a phylogenetic dimension. The outline above is based on Cajal's description of mammalian retinae and Polyak's work on primates. De Testa[20] has described four classes of amacrine cells in the fish: stellate, piriform, interstitial, and displaced. The stellates form a layer immediately internal to the internal horizontal cells. They are star-shaped, exhibit no axons, and their several dendritic extensions branch in all directions. These extensions divide into "octopus-like" branches, which extend externally and twist themselves about the bipolars. The cell bodies of the piriform class are found immediately below the stellates near the inner plexiform layer. De Testa notes two subclasses of this class; the "neuronal" subtype exhibits a long axon which runs tangentially at the external margin of the inner plexiform layer, and the "glial" subtype sends down a thick extension that divides in the inner plexiform layer.

The interstitial and displaced amacrines are found at the external and internal limits, respectively, of the inner plexiform layer. These cells are unusually large and tangentially oriented, and apparently have no axons. They exhibit thick and scanty extensions which become thin at their extremities. The dendritic trees form a dense network that extends throughout the inner plexiform layer.

Villegas also noted the glial-type amacrine in the fish,[21] but reports not observing it in the human.[8]

Dowling,[25] examining with the electron microscope the retinae of various vertebrates, including primates, reports not being able to discern subtypes of amacrine cells.

Ganglion Cells

Ganglion cells form the innermost cellular layer of the retina, and their axons constitute the optic nerve. Their activity may be viewed as the culmination of retinal information processing and the mode by which stimuli are presented to higher centers. Their electrical activity has been extensively recorded under a variety of conditions[1] and their histology has been rather thoroughly examined.

Dogiel[2] has delineated three classes of ganglion cells on the basis of the area covered by dendritic branching, the character of the dendritic branching pattern, and the level of the inner plexiform layer in which the dendritic arborization occurs. His classes are: (1) large cells (cell body diameter about 20 to 70 microns) with a very loose dendritic arborization containing three to twelve long branches which ramify in the innermost layer of the inner plexiform layer; (2) medium-size cells (cell-body diameter about 20 to 30 microns) with about one to four short and rather thick processes that penetrate about one-third of the inner plexiform layer before ramifying; and (3) small cells (cell body diameter about 10 to 30 microns) which exhibit one to three very short processes that ramify near the external level of the inner plexiform layer.

Cajal[3] has classified ganglion cells primarily on the basis of the level of the inner plexiform layer in which the dendrite branches ramify, and describes three major classes: (1) large ovoid cells exhibiting one or more dendritic stems with arborizations in the external layers of the inner plexiform layer; (2) small, oval cells exhibiting dendritic stems that form a delicate undulating horizontal arborization in the extreme external layer of the inner plexiform layer; and (3) medium-size cells exhibiting many dendritic stems that ramify into very dense and varicose arborizations in the external levels of the inner plexiform layer.

Cajal describes other types of ganglion cell based on other combinations of size, arborization type, and level of ramification. These include diffuse cells whose dendrites ramify in all levels of the inner plexiform layer or in two different levels.

Polyak[4] classified primate ganglion cells on the basis of their manner of dendritic branching.* He describes two major groups: individual and diffuse. The individual cells, of which only one type occurs, he calls "midget." These have a small oval or spherical cell

*Van Buren[26] points out that in practice Polyak avoided the use of the region in the inner plexiform layer in which arborization occurs as a criterion for classification. Polyak reported this to be a variable and inconsistent feature of any given cell type.

body, and a thin dendritic process that terminates with a few secondary and tertiary branchlets in a small "basket" whose diameter is less than the diameter of the cell body.

The diffuse group contains five diverse subclasses, which Polyak describes as follows:

1. Umbrella or Parasol. These have a medium-to-large, approximately spherical cell body, and exhibit one or more main dendritic stems that divide into very flat and dense arborizations.
2. Shrub. These have a relatively small body and exhibit a loose dendritic arborization composed of a few thin, twisted branches that terminate in contorted, hook-shaped twigs.
3. Small diffuse. These are quite small and exhibit a very loose dendritic tree composed of a few long branches that spread horizontally and obliquely.
4. Garland. These cells have a medium-size body with a few main dendritic stems that divide into a small number of thin secondary, and sometimes tertiary, branches. Their dendrites are the longest ganglion-cell dendrites observed by Polyak; they undulate laterally for long distances in the inner plexiform layer.
5. Giant. These cells are similar to the parasol and garland types, but are much larger.

Van Buren[26] has recently performed an extensive investigation of the histology of the ganglion-cell layer, which he summarizes as follows:

> Our attempts to stain the processes of the small ganglion cells within the central area with methylene blue met with no certain success as apparently had been the fate of our predecessors. Further peripherally, both in monkey and chimpanzee, we were able to unequivocally distinguish two major dendritic patterns. The first was of a cell of large size with dendrites of great length, usually few in number and showing relatively infrequent branching. This type was also identified in our two cases of intravitally stained human retinae. The second type noted in the lower primates, but not in our poorly stained human material, had a far less extensive dendritic tree top and showed an extensive local arborization

> of a most complicated type. Thus, in general, we would agree with Dogiel's view although I was unable to distinguish between his two smaller forms in our material so have, of necessity, omitted this subdivision.

Several recent investigators have suggested that cat ganglion cells may be classified as large or small on the basis of cell body diameter.[27-29] However, Stone,[27] who obtained histograms of the frequency of cat ganglion cells of different sizes, found that "the giant ganglion cells did not form a second mode in these histograms despite the fact that inspection of whole-mount preparations strongly suggests that they form a separate class." Stone also made a few observations on the monkey and noted that "no cells comparable to the giant cells of the cat retina are apparent, and the ganglion cells appear generally more homogeneous in size and staining than in the cat."[27]

Brown has suggested that in the rat[30,31] and the cat,[24] ganglion cells may be classified into two groups on the basis of dendritic-field diameter. According to Brown, large and small dendritic fields tend to correspond to large and small cell bodies, respectively. In the rat, the small dendritic fields exhibit tight, and the larger, loose, branching patterns. In the cat, the dendritic field diameters are 70 to 200 microns and 400 to 700 microns, respectively.

Electronmicroscopic examination has contributed little to ganglion cell classification. For example, Dowling[32] believes that the only pertinent classification comprises two groups, midgets and nonmidgets.

Since the fibers of the optic nerve are axons of ganglion cells, the classification of the diameter of optic fibers may be related to other modes of ganglion cell classification. As conduction speed is generally proportional to the square root of fiber diameter, the former may also be used as a measure of diameter. The results of several investigations utilizing either conducting velocity or direct fiber-size measurements, are inconclusive. Investigators have suggested two,[33] three,[34] and four[35] peaks in the size-distribution of optic fibers.

Concluding Remarks

Thus the extensive variety of cells in the retina appears amenable to systematic classification, although there is disagreement

over the most meaningful histological classification. There are also indications of some phylogenetic differences, especially among horizontal and amacrine cells.

The salient features of the foregoing descriptions of cell classification are summarized in part E of this section. In the remainder of this section we consider histological studies of the densities and distributions of the retinal cells and of their interconnection patterns.

B. DENSITIES AND DISTRIBUTIONS OF CELLS

The total surface area of the retina may be approximated by regarding the retina as partly covering the surface of a sphere (see Fig. 1), in which case we may write

$$A = \int_0^{\theta_1} \int_0^{2\pi} r\,d\varphi\, r \sin\varphi\, d\theta = 2\pi r^2[1 - \cos\theta_1] \qquad (1)$$

Table 1 shows the appropriate retinal radii for several species, the corresponding area calculated from Eq. (1) (assuming that $\theta_1 = 115$ deg), and the measured retinal area for the human and the cat.

Table 1

RETINAL SURFACE AREAS

Animal	Radius, mm	Area (from Eq. (1)), mm^2	Area (measured), mm^2
Human	11.0	1080	950[26]
Gorilla	11.0	1080	...
Chimpanzee	9.5	810	...
Rhesus macque	8.5	650	...
Cat	9.5	810	730--800[27]

Figure 4 contains the topographical distribution of rods, cones, bipolars, and ganglion cells for the human and of ganglion cells for the cat. The measurements on human receptors (Fig. 4a) were performed

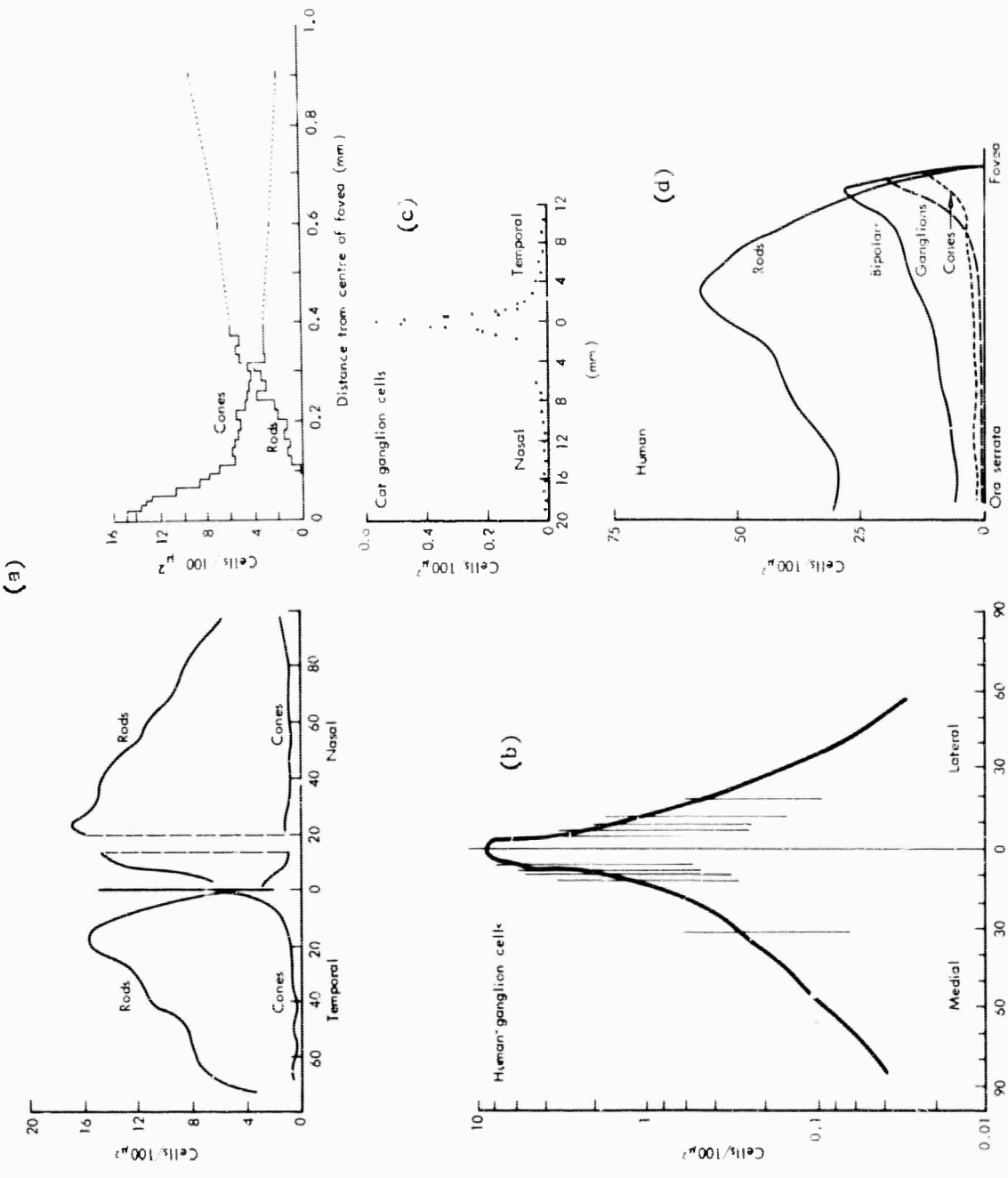


Fig. 4 -- Topographical distribution of retinal nerve cells.

by Osterberg,[36] and those on human ganglion cells (Fig. 4b) by Van Buren,[26] the cat ganglion-cell data (Fig. 4c) were reported by Stone,[27] and the human data (Fig. 4d) by Vilter.[37]

No quantitative data on horizontal or amacrine distributions have been found. Gallego[18] estimates the density of horizontal cells in the cat retina to be about 130/mm^2 in the periphery and about 270/mm^2 more centrally. Dowling[25] suggests that perhaps as many as one-fourth of the cells in the inner nuclear layer may be amacrines. Many investigations* show that horizontals and amacrines are present in large numbers throughout the retina, and that both classes tend to mingle their fibers with neighboring amacrines or horizontals to form a plexus or net, through which pass vertically oriented fibers.

Rods tend to become thicker and shorter in the periphery, and cones become shorter.[36] Foveal cones are longer and thinner than those at the periphery.[36] Polyak[4] reports that his mop, brush, and flattop bipolars are present "in great numbers" throughout the retina, although mop bipolars are not found in the central fovea. Midget bipolars, on the other hand, are present in the central fovea in a one-to-one correspondence with foveal cones. In peripheral regions the distance between midget bipolars increases greatly -- perhaps by a factor of, say, 25, to judge from Polyak's remarks.**

Villegas reports that "one of the three nuclear types described in the bipolar cell layer [see p. 12 above] was not observed in the parafoveal region of the monkey."[21]

Several investigations reveal a tendency for ganglion cells to become larger in the retinal periphery. Polyak[4] notes that his midget ganglion cells are much more dense in the fovea than in the periphery, and that his giant diffuse ganglion cells are found only in the far periphery.

Van Buren[26] reports that ganglion cells are small out to 5 deg from the fovea (8 to 10 microns in diameter), with a considerable number of larger cells appearing between 5 and 10 deg from the midfovea. Beyond this region the number of identifiable larger ganglion cells increases.

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*See Refs. 3, 4, 18, 20, 21, 25.

**See pp. 233-234 of Ref. 4.

Gallego[18] describes the distribution of dendritic spread in giant cat ganglion cells as follows: In the central zone most cells have dendritic fields of the same size as their cell body; that is, about 1.2 to 15 square microns; others, however, exhibit fields with diameters up to about 160 microns. Just outside the area centralis, some fields have diameters of about 25 microns, and most are about 80 microns. Between 4 and 6 mm from the center field, diameters are usually about 450 microns, and in the extreme periphery between 1/2 and 1 mm.

Polyak[4] reports that the size of horizontal cells gradually increases toward the periphery, as does the length of their dendrites and the number of baskets, until in the far periphery the cells attain a giant size (total lateral spread more than a millimeter) and have several dozens of baskets. Gallego[18] reports that the axon-less horizontals of the cat are smaller in the central region, with body dimensions of 6 × 9 microns and a total lateral expansion of 76 × 89 microns, than in the periphery, where the body dimensions are 7.5 × 12 microns and the lateral extensions, 92 × 116 microns.

The above considerations lead to an estimate, for the human retina, of about 6 million cones, 115 million rods, 12 million bipolar cells, and 2 million ganglion cells. A primary feature of the topographical distribution is the specialized foveal region. The highest density of cones in the rod-free area is about 16 per 100 square microns, for a total of about 34,000.[36] There are no ganglion cells[26] in the fovea per se; those that serve the central cones are offset and form a little ridge around the area. Their density approaches a maximum of about 8 per 100 square microns, and the cells are piled into tiers or layers. Immediately adjacent to the fovea are about five layers of ganglion cells. It is difficult to say how many of the central ganglion cells are associated with the foveal cones and how many are related to those receptors slightly outside the fovea. The total number of ganglion cells within 10 deg of the foveal center is about 700,000. Thus, the central 3 percent of the retina supplies about 40 percent of the optic nerve fibers. Bipolar cells are also very dense in this area.[37]

There is some topographical variation in the periphery. A typical region might have a cone density of 0.5 per 100 square microns, a rod

density of about 8 to 10 per 100 square microns, a ganglion cell density of about 0.2 per 100 square microns, and a bipolar cell density of 1.2 to 2.5 per 100 square microns. Thus, a bipolar cell whose dendrites extended 20 microns (total lateral extent of about 40 microns) would extend over a lateral area encompassing about 7 cones, 125 rods, and 20 to 40 other bipolars. If its dendrites extended to, say, 40 microns in length, these numbers would be quadrupled.

A ganglion cell whose dendrites extended some 200 microns in length would extend over an area encompassing about 240 other ganglion cells, about 1200 to 2800 bipolar cells, about 600 cones, and about 10,000 rods.

The difficulty faced by the microscopist attempting to unravel the interconnections among the cells is illustrated by a consideration of the density of dendritic processes in the outer plexiform layer. If there are about 1.5 bipolars per 100 square microns and if each bipolar exhibits, say, 7 processes, each of which extends laterally for about 20 microns, then each 100 square microns in the outer plexiform layer will contain portions of some 50 or 60 dendritic processes, each about 0.5 micron in diameter.

Electrical and histological information suggests that the retinal organization of the cat and the primate are similar. However, some differences are apparent, especially in the specialized central region. The area centralis of the cat is indeed specialized,[27,28] but does not seem comparable to the primate fovea.[28] Stone,[27] for example, suggests that ganglion cells in the central area of the cat are much less numerous, less homogeneous, and perhaps less specialized than those of the primate fovea. There is no definitive description of bipolar and receptor cells in the central area of the cat. Furthermore, the cat retina contains about 90,000 ganglion cells,[27] and the primate retina about 2 million. A comparison of Figs. 4b and 4c shows that the spatial distributions in the primate and cat are comparable but differ in density by a factor of about 10 throughout the retina.

We now turn to a consideration of the interneuronal connections in the retina.

C. INTERCONNECTIONS

The topic of retinal interconnection patterns is not closed, and indeed is the focus of extensive current work with the electron microscope. Polyak[4] has described quite explicitly the mode of interconnection of neural elements, but his statements have not always been corroborated by electron microscopy. Nonetheless, Polyak's position will be described in detail here with the understanding that current work may invalidate any particular part of it.

Polyak's description suggests a primarily vertical organization in which fundamental pathways progress from receptors to bipolars to ganglions, with superimposed lateral influences mediated by horizontal and amacrine cells.

Each receptor connects with several bipolars.* Cones connect to each of several mop, brush, and flattop bipolars, and perhaps to one midget bipolar. Rods may go to brushes, flattops, and mops, but the majority are connected only to mops. Each bipolar, on the other hand, is connected to several receptors. Midget bipolars connect to cones only, to whose vitreal surfaces their dendritic bouquets are adjacent. In the fovea each midget bipolar has one bouquet which connects to one cone; in the periphery some midgets exhibit two or three bouquets which attach to as many cones. Brush and flattop bipolars are connected to both rods and cones. These connections are to the vitreal surface of the receptors, and the individual dendritic arborizations cover about six cones in the fovea and about three cones in the periphery. Mop bipolars connect to the sides of both cones and rods. Their dendritic arborizations cover about six cones. These cells are absent from the central fovea.

Most bipolar cells connect to several ganglion cells. The midget bipolar connects with a midget ganglion, placing its clumpy axonal

*Receptor connections with subsequent cells exhibit the typical anatomical features of synapses.(6,8,21.38-41) A slight deviation is that receptor presynaptic regions contain "ribbons" as well as the typical synaptic vessicles. Furthermore, the geometry of these junctions is somewhat atypical: the postsynaptic processes extend into invaginations in the receptors.

terminations in the latter's dendritic basket, but synapses on the dendrites of different ganglion cells as well. Brush and flattop bipolars synapse with dendrites of all ganglion types, apparently indiscriminately. Each connects with perhaps two or three ganglion cells. The mop bipolar, on the other hand, makes axo-somatic synapses with from one to four ganglion cells. However, the mop axon also exhibits one or two twigs that may make axo-dendritic connections with ganglion cells. Both types of connections are made indiscriminately to all ganglion cell types.

Midget ganglion cells connect axo-dendritically with one midget bipolar, forming from four to six brush and flattop bipolars in the fovea, and with two to three brush and flattops in the periphery. The midget ganglion cell does not connect with mops in the fovea, but connects axo-dendritically with one mop in the periphery. Each diffuse ganglion cell connects axo-somatically with one mop in the periphery. Diffuse ganglion cells are connected axo-dendritically to many midget, brush, and flattop cells. The number of connections is determined by the extent of the ganglion cells' dendritic spread. If there are about 1.5 bipolars per 100 square microns, about three bipolar-ganglion connections per bipolar, we can estimate that for a ganglion cell density of about 0.2 per 100 square microns there are about twenty-five bipolar-ganglion connections per ganglion. This number is merely a crude estimate; the larger dendritic fields may contain many more connections and the smaller ones somewhat fewer.

The horizontal-cell dendrites exhibit little baskets that connect in a one-to-one correspondence with the vitreal surfaces of the cones. In the central fovea each horizontal connects to about six cones or less, whereas in the periphery of a single horizontal may exhibit several dozen baskets, each of which apparently connects to a single cone. The axons, which are several hundred microns long, terminate in arborizations that cover an area considerably larger than the dendritic spread and connect to both rods and cones.

Polyak does not explicitly delineate amacrine-cell connections, mentioning only that their dendritic arborizations spread through the inner plexiform layer, with their lowermost twigs sometimes touching the bodies of ganglion cells.

Thus Polyak provides a relatively well-defined organization of the primate retina. The schematics in which he summarizes his work are shown in Fig. 5; unfortunately, their accuracy is not presently established. Most probably his assessment is reasonably reliable in most respects. Several features, however, particularly with regard to lateral influences, do not seem entirely consistent with electronmicroscopic studies.

Recent electronmicroscopy has revealed direct interconnections among receptors.* Sjostrand[40] reports that lateral processes arise in receptors in the guinea pig and form one of two types of interreceptor connections. The first type connects with an adjacent receptor and the second with a receptor some 7 to 10 microns away.

Missoten[6] has described connections between rods and cones in the human. These consist of a process arising in the cone peduncle and penetrating the rod ending. The synapse at the rod has the same morphology as those between the rod and bipolar processes. Villegas[8] has also seen processes extending laterally from cone endings in the human extrafoveal region. She was not able, however, to follow them to their terminations.

Several investigations with the electron microscope seem to be essentially consistent with Polyak's description of the outer plexiform layer. Villegas[8,21] has reported that about ten processes invaginate cone endings, whereas rod endings are penetrated by only one process. Missoten[6] has reported that each rod exhibits only one invagination, each containing two or three dendrites.

In marked contrast to these reports are the findings of Pedler, who reports that "it is easy to find complex pedicles with up to 300 separate neurites making contact with the synaptic surface."[42] Pedler also distinguishes between two types of receptor-bipolar synapses.

The connections of horizontal cells have not yet been established by electronmicroscopy. Villegas has been unable to trace horizontal processes to their terminations. She does describe, however, "...cross-membrane contacts between themselves [horizontal processes], and also

*See Refs. 6, 8, 39, and 40.

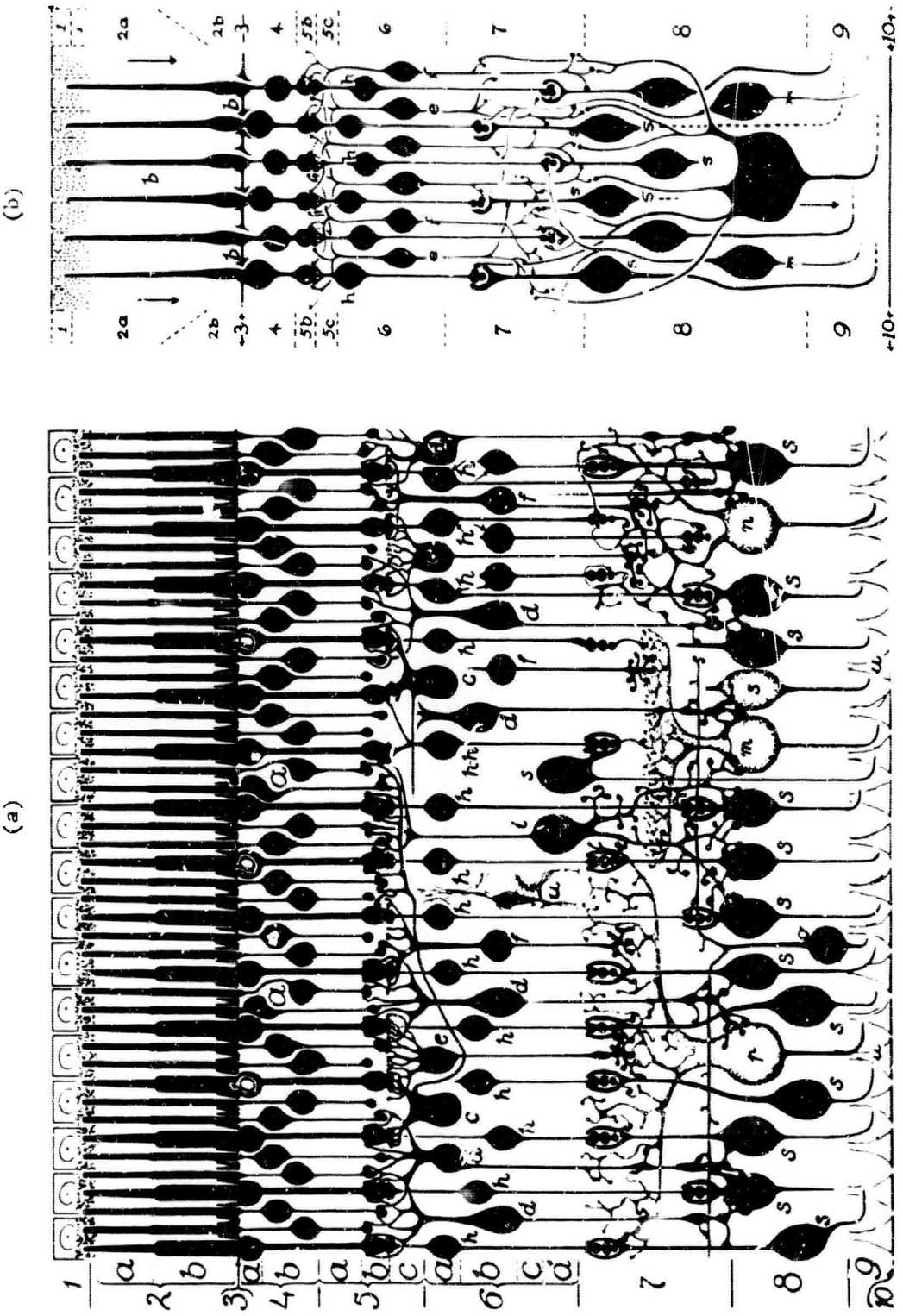

Fig. 5 -- Polyak's schematics of retinal organization: a. periphery, b. fovea (by permission from S. Polyak, The Vertebrate Visual System, The University of Chicago Press, 1957).

with the bipolar cell processes as well as with the bipolar cell bodies."[8] Villegas emphasizes the lateral plexus formed by the horizontal processes, and reports that in the fovea horizontal processes do not intertwine in the neuropile. Sjostrand[40] also has been unable to follow horizontal processes.

Pedler,[42] on the other hand, reports that horizontal cells synapse on receptors. Unfortunately, he does not say whether the receptor-to-horizontal connections arise only from cones. Pedler also reports consistently finding foveal bipolars whose dendritic domain diameter extends over approximately three cones.

Electronmicroscopic investigations of the inner plexiform layer, on the other hand, reveal interconnections that seem somewhat more complicated than described by Polyak. Kidd,[43] investigating the inner plexiform layer of the cat and the pigeon, describes four types of synapses:

1. Conventional. These are the most common, and Kidd notes both Type I and Type II. (Observers have hypothesized that these correspond to excitatory and inhibitory synapses, respectively; see Section III.) Conventional synapses occur with a density of about 0.2 per square micron in the cat.
2. Spine. These are less numerous than the conventional type and are characterized by a postsynaptic process lying within a presynaptic invagination.
3. Ribbon. These contain a ribbon in the presynaptic process, and often occur at a junction of three processes, two of which are postsynaptic.
4. Serial. Kidd describes two varieties of these. One consists of a presynaptic process that synapses conventionally with a process containing ribbons. The second consists of a process presynaptic to a second, which is presynaptic to a third, all of which are conventional. Kidd notes that serial synapses occur much more frequently in the pigeon than in the cat, and points out that the pigeon also has a higher proportion of amacrine cells. He did not attempt to identify the various processes with cell types.

Dowling,[25] on the other hand, reports being able to differentiate between bipolar and amacrine processes in the retinae of various vertebrates, including primates. He finds ribbons only in bipolar cells and describes synaptic arrangements very similar to the serial synapse described by Kidd. The bipolar process synapses simultaneously on two processes, one of which is a ganglion-cell dendrite and the other an amacrine process. Sometimes this amacrine process synapses on a fourth process, such that the original bipolar--amacrine connection is presynaptic. In other instances the amacrine-cell processes synapse presynaptically on a bipolar terminal, and sometimes an amacrine process of the bipolar-amacrine-ganglion junction is seen to synapse directly back on the original bipolar process. Synapses between two bipolar processes were sometimes observed.

Axo-somatic synapses between bipolar processes and ganglion cells were found by Dowling to be much tighter (i.e., had a much smaller synaptic cleft) than is normal. No axo-somatic contacts were found in the rod-free region.

These observations are of some interest because they immediately suggest the neurophysiological mechanism of presynaptic inhibition and the possibility of electrical interneuronal transmission (see Section III).

Thus some investigations of the outer plexiform layer seem to be quite consistent with Polyak's description, and others less so. The inner plexiform layer, in particular, seems to be more complicated than Polyak's description suggests.

Retinal interconnections are by no means established, and are currently the focus of intensive research. R Allan and F. Sjostrand, for example, are thoroughly investigating this topic.[44]

D. EFFERENT INFLUENCE

Several factors suggest that efferent fibers influence retinal activity. First, most other sensory channels incorporate efferent mechanisms,[45] which are mediated primarily by presynaptic inhibition (see Section III) on primary afferent nerve cells. Electrical evidence has

been somewhat ambiguous,[1] indicating at most only weak excitatory and inhibitory effects. In general, fiber counts in the optic nerve compare favorably with ganglion-cell counts;[46] for the primate, Van Buren[26] counts more ganglion cells (2 million) than Bruesch and Arey[47] count optic fibers (1 to 1.2 million). However, Maturana[48] has recently suggested that the electron microscope may reveal fine efferent fibers not readily observable with the light microscope. Taking other sensory channels as a guide, we might expect precisely the small-diameter fibers to carry efferent activity.[49]

Degeneration studies[50-52] also suggest efferent influences. Finally, the possible stimulation of spontaneous activity by the reticular formation of the brain stem presumes the existence of efferent fibers.

If efferent influences do occur, it is not clear where they act. The most plausible working hypothesis is that they act in the inner plexiform layer and perhaps mediate a presynaptic inhibition on axonal end feet of bipolar cells.[52]

E. SUMMARY

Five main classes of neural elements are found in the retina: receptors, horizontals, bipolars, amacrines, and ganglions. Their orientation and topology are illustrated in Fig. 6.

A very large number of subclasses of these cells has been defined on the basis of size, connection patterns, dendritic branching patterns, location of arborizations, and other histological features. Most of the subclasses described in Part A are shown in Fig. 3.

Cells are relatively dense throughout the retina, particularly near the fovea. The topographical distribution of rods, cones, bipolars, and ganglions is shown in Fig. 4. Fibers from adjacent cells overlap considerably, as illustrated in Table 2a, which represents a "typical" area in the periphery. Table 2b indicates the number of cones, bipolars, and ganglions within 10 deg of the fovea center. The density of amacrine and horizontal cells may be about 0.4 per 100 square microns.

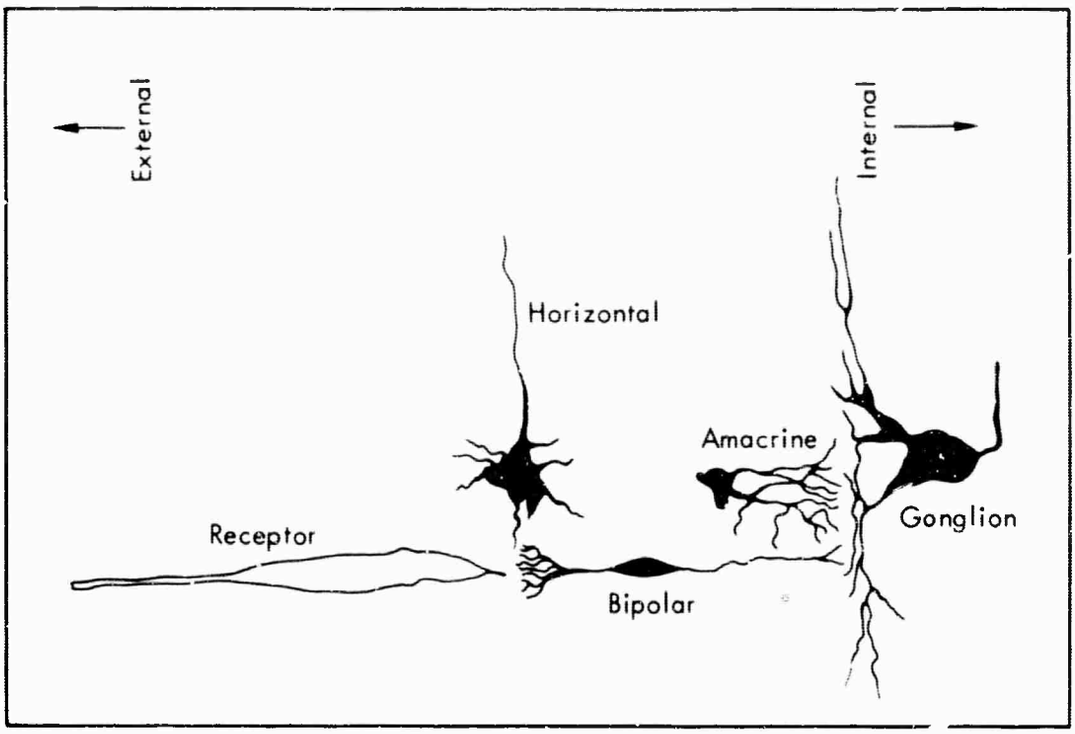

Fig. 6 -- Five main classes of retinal neural elements.

Table 2

APPROXIMATE DENSITIES OF RETINAL NEURAL ELEMENTS

	(a) Periphery			(b) Fovea
Cell Type	No. per 100 μ^2	No. Within Bipolar Dendritic Span of 40 μ	No. Within Ganglion Dendritic Span of 400 μ	No. Within 10^o of Fovea
Cone	0.5	7	600	0.87×10^6
Rod	8-10	125	10,000	2×10^6
Bipolar	1.2-2.5	20-40	1200-2500	2×10^6
Ganglion	0.2	...	240	0.7×10^6

Polyak[4] has offered a relatively complete description of the complicated interconnections among retinal cells, summarized in Fig. 7. Electronmicroscopy, however, suggests that even Polyak's scheme may be somewhat oversimplified. Among other complications, direct connections between rods and cones have been reported. Also, reported ratios of neurites per receptor range from 1 for rods and 10 for cones to up to

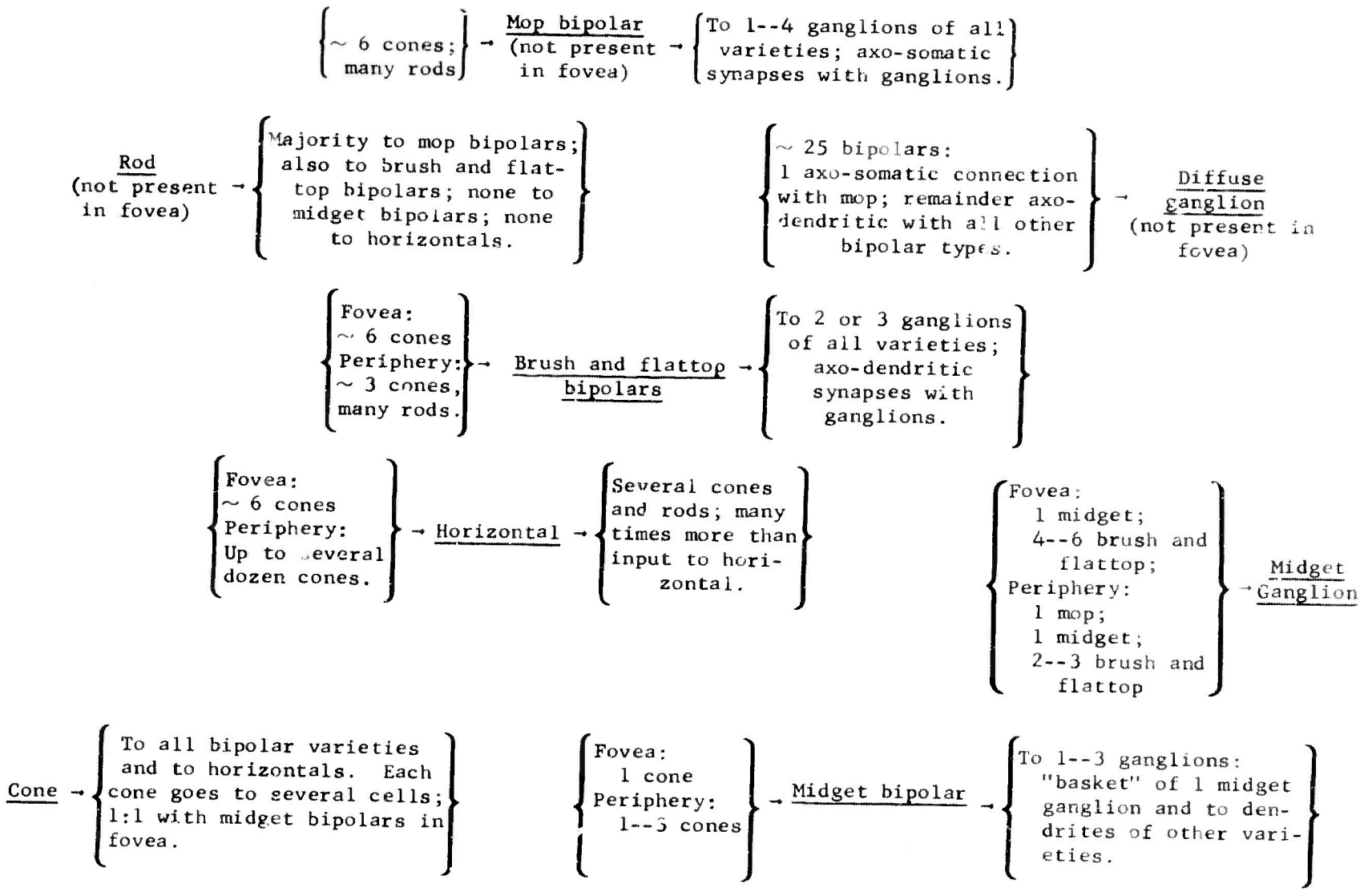

Fig. 7 -- Retinal organization as described by Polyak. The schematic shows the connections to ({ } → x) and from (x → { }) a typical member of the class indicated by underscored (x).

300 for complex pedicles. Most workers have not been able to follow the processes of the neuropile in the outer plexiform layer with any certainty. Horizontals have been reported to connect to receptors, but also to bipolar cells.

Several different types of synapses have been reported in the inner plexiform layer, including an unusual "serial" synapse. Unusual connection patterns are found extensively in the inner plexiform layer, and most typically incorporate processes of amacrine cells.

The extent of efferent influence, its locus, and mechanism of action are not known.

III. NEUROELECTRICAL AND NEUROPHYSIOLOGICAL ELEMENTS

This discussion will present rudiments of those features of neuroelectrical recordings that reflect retinal organization and of neurophysiological mechanisms that underlie neural behavior. Portions of both these topics are treated in more detail by the author in Refs. 1, 53, and 54.

A. NEUROELECTRICAL

We may distinguish two classes of neuroelectrical recordings pertinent to the present task: recordings from the easily accessible optic nerve fibers (ganglion-cell axons) and intraretinal recordings obtained with microelectrodes. The vertebrate electroretinogram (ERG) has been extensively investigated under a variety of conditions, but as it involves the combined activity of many cells, its relation to retinal organization is not readily apparent.

Ganglion Cell Spike Trains*

The properties of the spike trains of cat ganglion cells have been thoroughly investigated. Primate ganglion cells, on the other hand, have undergone only preliminary investigation, and there are no data from these cells in the fovea. Nonetheless, the evidence does suggest that organization in the periphery of the primate and cat retinae are quite similar.

A significant feature of ganglion-cell behavior is spontaneous activity. That is, the cells fire more or less at random in the absence of any illumination.

The distinction between "on-" and "off-" responses forms the basis for a convenient neuroelectrical classification of ganglion cells. Each ganglion cell gives on type of response when a small core region on the retina is illuminated, and the opposite type from an annular region surrounding the core. Simultaneous stimulation of portions of

*The data presented here are abstracted from a more detailed account given in Ref. 1.

both regions results in a mutual inhibition of the two types of responses; thus the annulus is called the "opposing periphery." Significantly, in both cats and primates the opposing periphery is ineffective in its dark-adapted state. The core diameter is approximately 300 to 600 microns in primates, and the external diameter of the opposing periphery is about 1 to 2 mm.

Cells with off-cores tend to have a slightly larger core diameter, respond with a shorter latency, respond maximally to a higher frequency of sinusoidal illumination, and exhibit a higher rate of spontaneous firing than do cells with on-cores.

The number of on-cores is approximately equal to the number of off-cores in both the centralis and the periphery of the cat retina, but Fig. 8 suggests that on-cores may predominate in the primate fovea. Core diameters decrease near the central area in both cat and primate retinae.

Cells exhibit on-, off-, or on-and-off responses to diffuse light, depending on the relative strengths of the core and peripheral influences. The off-response to diffuse light always comes from an off-core unit; the on-and-off response may come from either type of core, but is more commonly obtained from off-cores.

The firing frequency of ganglion cells exhibits a sigmoid dependence on the logarithm of stimulus intensity, and is approximately proportional to the logarithm of [illegible] tensity over a range of about 2 to 3 log units.

Intraretinal Recordings

Electrical recordings taken within the retina are much less numerous than the ganglion cell recordings discussed above. Brown and Wiesel[56] investigated the cat retina and obtained single-unit responses in the ganglion cell layer, the inner nuclear layer, and just external to the inner nuclear layer. The recordings from the inner nuclear layer were presumably taken from bipolar cells, and are therefore of considerable interest, as no other recordings from these cells have been reported. The inner nuclear recordings reflected spike activity, in contrast to the recordings obtained more externally, which

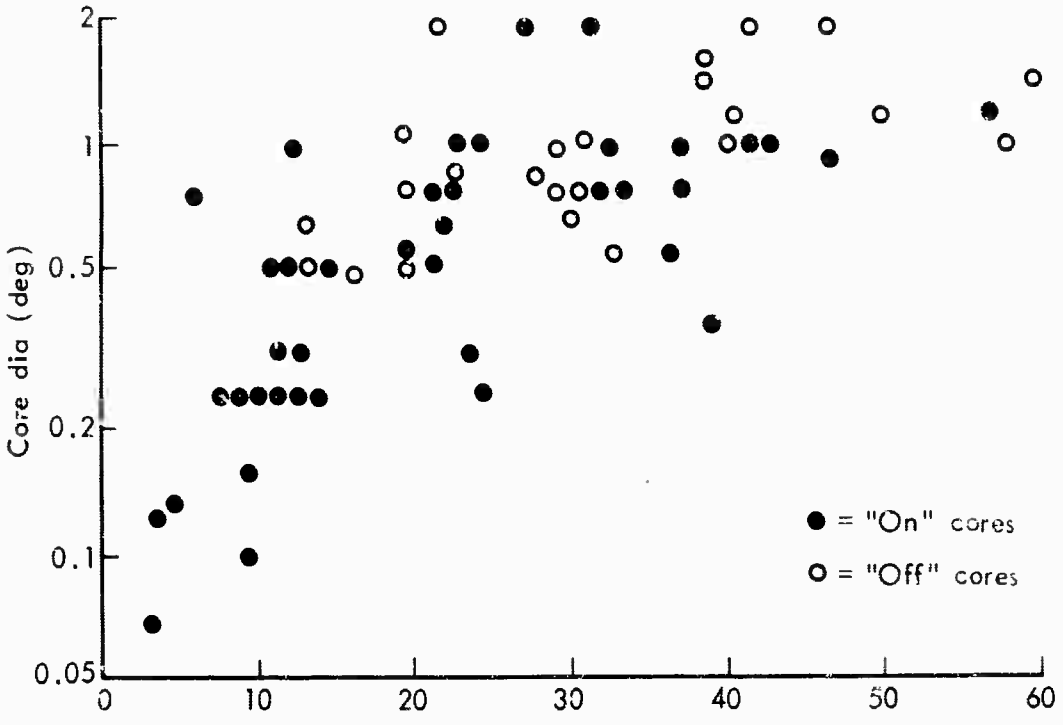

Fig. 8 -- Distribution of core diameters.[55]

reflected graded responses. Furthermore, spontaneous spike activity was observed in the inner nuclear layer. The receptive fields of the cells of the inner nuclear layer were functionally organized like those of ganglion cells, comprising on-core and off-core types, both of which exhibited opposing peripheries.

Brown and Wiesel also describe graded responses in units just external to the inner nuclear layer. All the responses were hyperpolarizations, i.e., showing increased negativity at the recording site. The response amplitudes ranged from 5 to 25 mv. Some were associated with a resting potential of -50 to -60 mv and some were not.

The graded potentials reported by Brown and Wiesel in the cat eye are very similar to those discovered recently in fish retinae. These so-called "S-potentials"* are of considerable current interest, as they seem to reflect physiological mechanisms intimately related to color vision. The S-potentials comprise two types, L-potentials and C-potentials. Both types are of the order of 5 to 30 mv, are continuous and

*Access to this literature may be obtained through Refs. 57 and 58.

graded, and depend on stimulus intensity, with small deviations according to $E \sim I/1 + I$. The recording site is sometimes characterized by a negative resting level of up to about -60 mv. The L-potentials are recorded near the level of the horizontal cells and are hyperpolarizations for all wavelengths. C-potentials, on the other hand, are recorded near the level of bipolar nuclei and are hyperpolarizations for short wavelengths and depolarizations for long wavelengths. Two subtypes of the C-potential have been described, one with peak responses at yellow and blue and the other with peaks at red and green.

Brown and Wiesel's description of the spike-producing cells of the inner nuclear layer of the cat retina is of considerable interest. Unfortunately, however, their work has yet to be reproduced or extended, and the possibility that they were recording from ganglion cells remains open. Comparable descriptions of S-potentials, on the other hand, have been reported by several investigators, and their properties seem to be reasonably well established.

One more class of intraretinal recordings comprises electrical potentials supposedly attributable to single receptors. Brown and Watanabe[13,14] have reported that potentials recorded near single receptors exhibit the time course shown in Fig. 9. A significant feature is that the cone response follows the time course of the stimulus very closely, whereas the rod response shows a marked lag, rising for some hundreds of milliseconds and taking a second or more to diminish.

A problem of theoretical interest, discussed below, concerns the dependence of receptor response on stimulus intensity. Fatehchand, Laufer, and Svaetichin[15] have precluded the behavior of retinal nerve cells by applying NH_3 to the fish retina and recording potentials across the receptor layer in response to illumination. They find two distinct responses, fast and slow, which correlate with light and dark adaptation, respectively, and thus supposedly represent cone and rod activity. The amplitudes of both types of response are related linearly rather than logarithmically to stimulus intensity. The threshold of the fast response is some 3 to 4 long units higher than that of the slow response in the dark-adapted state, and the slow response threshold increases during light adaptation.

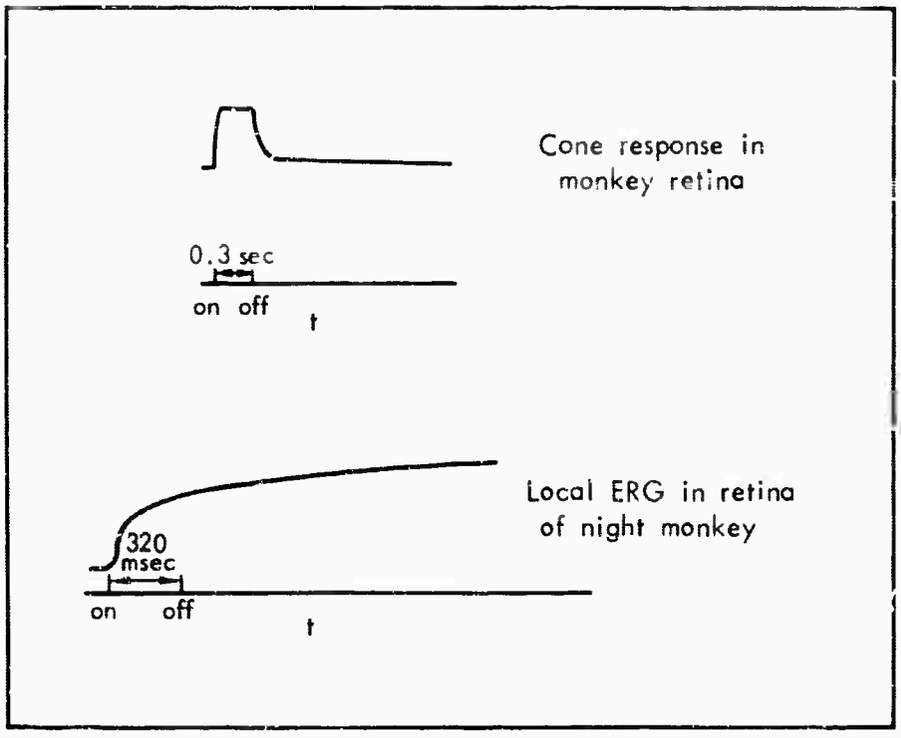

Fig. 9 -- Time course of receptor response to illumination.

B. NEUROPHYSIOLOGICAL

The most satisfactory generalization of the behavior of single nerve cells may be loosely termed the theory of the generating potential.* Its central hypothesis is that integrative processes occur at the input end of the cell through the interaction of graded potentials. The resultant of this interaction is converted at the soma into a series of all-or-none spikes, which are propagated without meaningful alteration to subsequent cells. The series of spikes thus represents a sampling of the graded potential, or "generating potential."

The process whereby spikes are elicited by the generating potential has been investigated extensively with computer models.** The nonlinearity of the process is largely restricted to fine-grained characteristics of the spike trains' temporal structure;(54)*** mean spike

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*See Refs. 53, 54, 59.

**See Refs. 53, 54, 60-63.

***The work of Segundo, Perkel and Moore(64) on this characteristic of neural function is particularly illuminating.

frequency is approximately proportional to the amplitude of the generator potential.[53,65]

In the remainder of this section we consider briefly those features of neural function that seem most pertinent to the interpretation of retinal behavior; first, the modes of interaction among nerve cells and some of their basic properties, and second, the physiologically significant dimensions of nerve-cell classification.

Modes of Interaction Among Nerve Cells

The commonest mode of communication[66] between nerve cells is synaptic (chemical) transmission, as illustrated in Fig. 10. The mechanisms and properties of synaptic activation have been extensively explored, both experimentally and theoretically. The occurrence of a spike in the presynaptic cell causes the release of a chemical transmitter that increases the permeability of the postsynaptic membrane. The resulting flux of ions through the membrane elicits an electrical potential in the postsynaptic cell. When the activity in the presynaptic cell is pulsatile, both the release of transmitter and the resulting postsynaptic response are pulsatile as well. Synapses are either excitatory (depolarizing) or inhibitory (hyperpolarizing), depending on the equilibrium potential corresponding to the change in postsynaptic permeability. The postsynaptic pulses are accordingly called excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs).

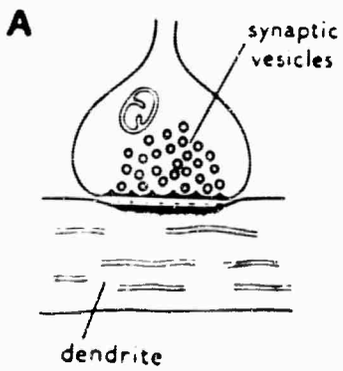

Fig. 10 -- The synapse.

There are indications that excitatory and inhibitory synapses may be differentiated on a histological basis. Thus, Eccles[56] lists four criteria for distinguishing type 1 from type 2:

> The synaptic cleft is wider (300 A) as against 200 A for type 2; the postsynaptic membrane is more thick and dense; the dense patch is much more extensive, occupying the greater part of the opposing synaptic membranes; and in the cleft there is a plaque of extracellular material nearer to the postsynaptic membrane.

Type 1 may be excitatory and type 2 may be inhibitory.

Both experiment and theory suggest that the properties of excitatory synaptic activation are different for axo-somatic and axo-dendritic synapses.[67,54,68] On the somatic membrane, EPSPs seem to sum linearly; transfer curves for axo-somatic activation and interaction among axo-somatic synapses are thus largely void of nonlinear characteristics.

Axo-dendritic activation, on the other hand, is characterized by a high degree of nonlinear interaction. The fundamental reason for the distinction appears to be that the magnitudes of synaptic potentials are significantly higher in dendritic regions than at the soma. Theoretical work has shown that the PSP associated with a given permeability change depends inversely on the square root of the neural radius,[54] thus suggesting that PSPs are larger in dendritic regions than in somatic regions.

The analysis of the properties of the generator potential may proceed whether the response in the dendritic membrane is linear or nonlinear. Theoretical work has been performed for both cases, and it appears that each is applicable to a different class of nerve cell.

Experimental work has shown that PSP interaction in invertebrate nerve cells is markedly labile. Bullock[69] has found experimentally that PSPs in these cells exhibit three degrees of freedom: (1) excitation or inhibition, (2) facilitation or antifacilitation, and (3) excitatory or inhibitory after-effects. These properties have been observed in a model made by Lewis[63] based on the nonlinear Hodgkin-Huxley equation. By assuming that the dendritic membrane differs from excitable membrane only in having a higher capacitance, Lewis finds that

the threshold is greatly increased so that spikes are not elicited, and further that all of the effects described by Bullock are obtained. A non-linear membrane, such as that observed by Bullock and modeled by Lewis, is exceedingly prone to oscillatory potentials.[70]

Most vertebrate nerve cells, on the other hand, are less labile.[71] The present author's theoretical treatment,[54] based on the assumption that the dendritic membrane responds linearly, seems adequate to describe much of the behavior of vertebrate cells. In this theory, nonlinearity is attributed to a synaptic mechanism whereby postsynaptic response is diminished by prior transsynaptic potential. Nerve-cell parameters are such that this mechanism is most marked for axo-dendritic activation. Figure 11 shows typical transfer curves for this theory.

The curve shown in Fig. 11b is characteristic of a continuously active synapse releasing a quantity I of transmitter. This curve is discussed in conjunction with intensity encoding in Section IV, Part C.

The combination of two or more excitatory inputs on different dendritic branches or on the soma results in an approximately linear superposition or slight facilitation, but a marked occlusion occurs (that is, the response to the combination is less than the sum of the individual responses) if they are on the same dendritic branch.

Another consequence of our formulation is that a sharp initial peak occurs in the response to stimulation on a previously inactive dendritic branch, and this peak may be markedly diminished by prior activity.

The properties of inhibitory synaptic activation do not seem to have been extensively explored. Eccles has suggested that inhibitory synapses may be solely axo-somatic.[66] It is easy to see that inhibitory synapses on dendrites would be exceedingly effective because the IPSP would be markedly increased by the large dendritic depolarizations. If Eccles's suggestion is valid, synaptic inhibition may be an approximately linear phenomenon. That is, one might approximate the total output frequency of an excitatory synapse activated at frequency ν_1 and an inhibitory synapse activated at frequency ν_2 by $E \sim A\nu_1 - B\nu_2$. However, an analysis might show significant nonlinear effects even for axo-somatic inhibitory synapses.

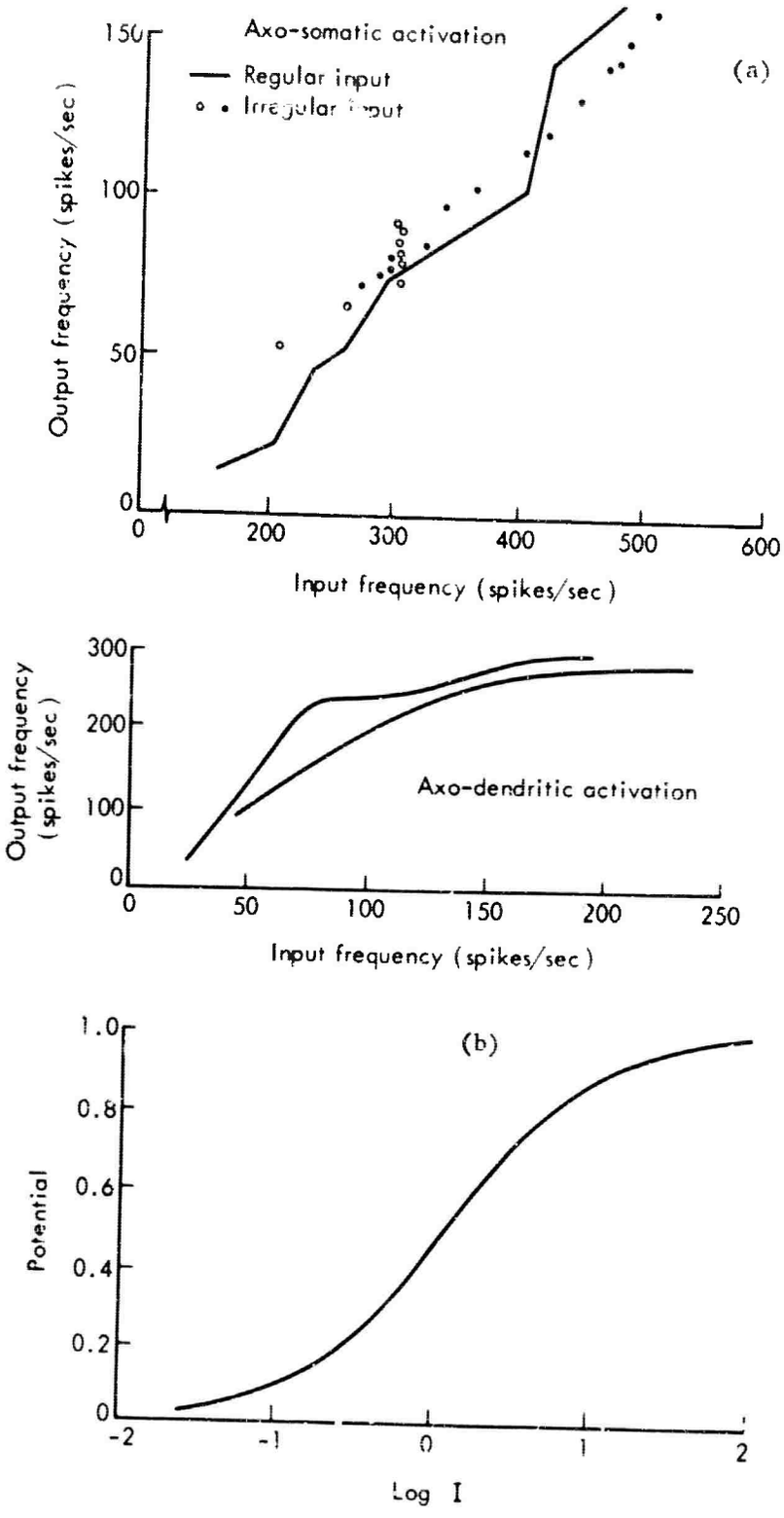

Fig. 11 - Theoretical nerve cell transfer curves.(53,54)

Some nerve cells exhibit plastic behavior; that is, their response to a given input changes gradually with time or depends upon past activity.[72,73]

Another basic mode of neural interaction is presynaptic inhibition (Fig. 12), which occurs ubiquitously in both primary afferent cells[66] and in the central nervous system.[1] It is effected by a synapse (a) on the presynaptic fiber (b), which when active elevates the potential of the presynaptic fiber (b). The increased presynaptic potential then diminishes the amount of transmitter released when the presynaptic cell is activated. The properties of this mechanism have been investigated thoroughly by Eccles,[66] who found that the diminution is effective for the order of 100 msec and that the quantity of transmitter released decreases exponentially with presynaptic depolarization.

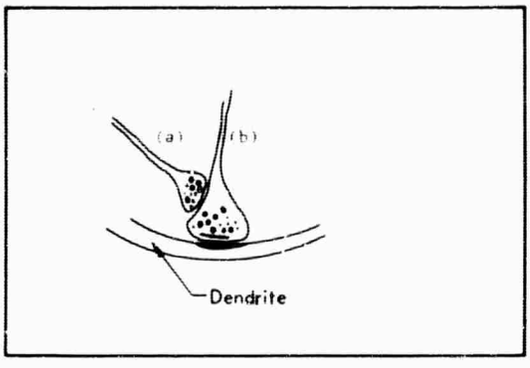

Fig. 12 -- Presynaptic inhibition.

In addition to synaptic interaction, some cells seem to interact electrically without chemical transmission.[74] Apparently no theoretical analysis of its properties has been done, but one suspects that the interaction would be linear.

In addition to direct electrical influences at intercellular junctions, nerve cell behavior may be modulated by an electrical field resulting from the gross activity of many surrounding cells. Such effects have been described by Nelson,[75] who estimates that a field of about 5 mv/mm may decrease the threshold of a spinal motoneuron to a given stimulus by as much as 10 to 20 percent. The extent to which this effect might occur in normal function is currently unknown.

Dimensions of Cell Classification

Several dimensions of cell classification are apparent from a consideration of neural mechanisms.

Early observations had generated the hypothesis that a given cell is either excitatory or inhibitory.[66] That is, all the synapses of a given cell on subsequent cells or effectors are either excitatory or inhibitory; a given cell does not elicit EPSPs on one cell and IPSPs on another. Recent work, however, has brought this generalization into question.[76] It is not clear whether histological evidence might reflect such specialization.

Another dimension is the interaction mechanisms which are emphasized by the geometry of a particular cell. The latter is determined primarily by the cell's dendritic branching pattern.[54] Two fundamental types, the radiate and the tufted, have been identified by Ramon-Moliner[77] (see Fig. 13). The tufted cell might be interpreted theoretically to involve a high degree of synaptic interaction and to be particularly sensitive to stimulus initiation. On this basis these cells would be expected to exhibit an occluded response to combinations of inputs. The radiate cells would exhibit less dendritic interaction than the tufted, and might be expected to sum responses approximately linearly.

The size of a nerve cell is also related to its properties.[54] Experimental evidence[78] indicates that small cells have larger PSPs than do larger ones, and thus are generally more excitable. Larger cells, on the other hand, conduct impulses more rapidly.

The degree to which a nerve cell habituates is an additional dimension of classification. Unfortunately, the mechanism of this effect remains unknown, and thus cannot be related to histological features.

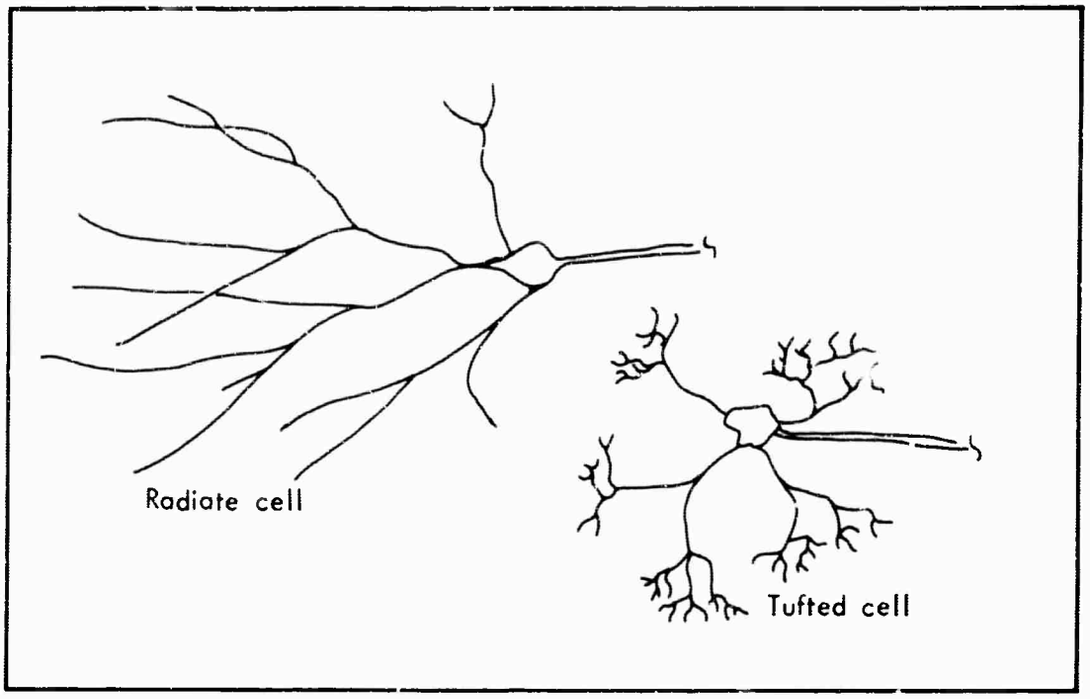

Fig. 13 -- Radiate and tufted cell types.

IV. OVERVIEW OF RETINAL ORGANIZATION

As illustrated in the following discussion, many problems frustrate a satisfactory understanding of retinal organization. This section highlights some of the major difficulties and provides a tentative organizational schema for initial theoretical work.

A. DISCUSSION

A salient feature reflected by neuroelectrical data is the division of ganglion-cell receptive fields into core and peripheral regions. A prima facie interpretation of the data suggests that the core corresponds to the lateral expanse covered by those bipolar cells that connect directly to the ganglion-cell dendrites, and that the periphery is mediated by lateral cells, probably horizontals (see Fig. 14). The appropriate histological dimensions and their topographical variation match those revealed by the neuroelectrical data quite well (see Section II and Fig. 8).

A fundamental point is that the core has been repeatedly reported to be homogeneous;[1] that is, one does not find off-responses from one portion of the core and on-responses from another, and to a first approximation, the responses sum linearly. This characteristic presents no difficulty in a purely excitatory pathway, and indeed, is precisely what would be expected in this case. It is somewhat difficult to interpret, however, in view of the combinations of inhibition and excitation prevalent in retinal function.

On- or off-responses are not intrinsic to a ganglion cell, but reflect the input. A consideration of the source (or sources) of off-responses and of the basis of the neuroelectrical classification of on- and off-cores will illuminate the difficulty presented by the homogeneous core.

The rubric of the "off-response" encompasses two response characteristics: (1) an inhibition of activity during illumination, and (2) an elevation of activity upon its cessation.

It seems likely that one or more inhibitory mechanisms are active in the inner plexiform layer. Polyak's report that mop bipolars synapse

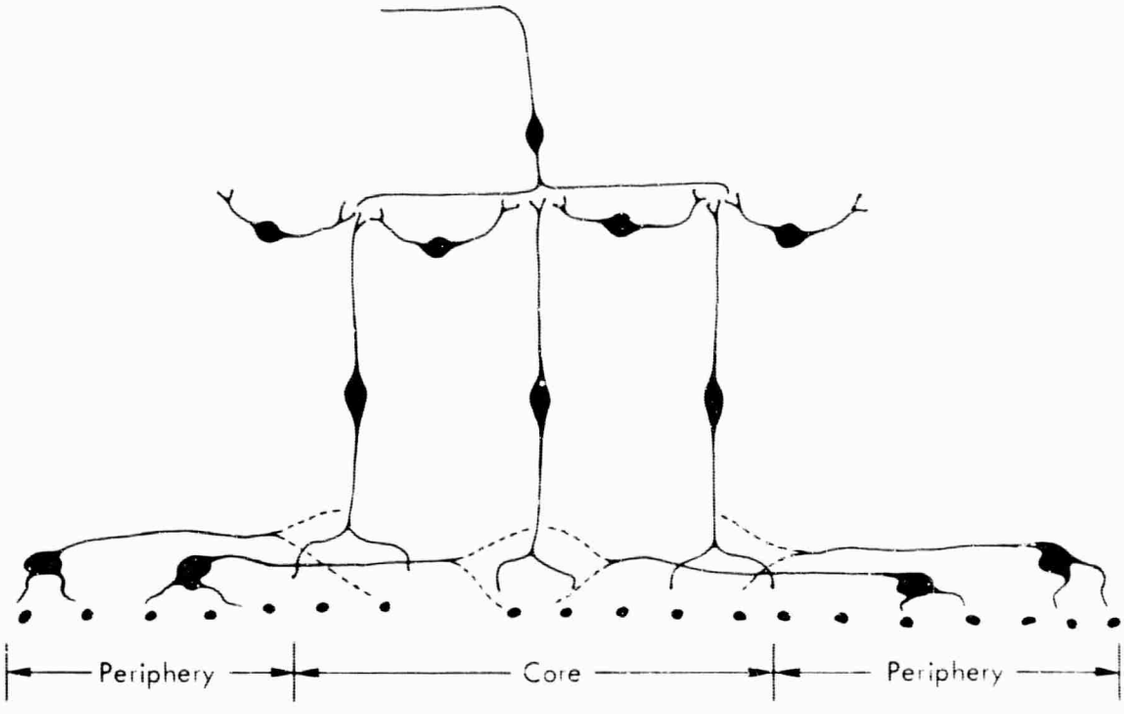

Fig. 14 -- The ganglion cell receptive field.

axo-somatically on ganglion cells (whereas those of the other bipolar types are axo-dendritic), together with Eccles's suggestion that inhibitory synapses are primarily axo-somatic, suggest the hypothesis that mop bipolars are inhibitory. This would be consistent with Kidd's observation of Type II synapses in the inner plexiform layer, with Villegas's observation that her third nuclear type of bipolar did not appear in the fovea (Polyak's mops are absent from the fovea), and with the fact that off-responses have shorter latencies than on-responses.

Amacrine cells may also have inhibitory effects. Dowling, for example, has suggested a presynaptic inhibitory role for these cells on the basis of their unusual junctions. Furthermore, there may be an inhibitory feedback from higher centers, mediated by efferent fibers.

Inhibition probably occurs distal to bipolar cells as well. As discussed in Part C, horizontal cells most likely inhibit laterally.

Two sources of electrical data suggest that, aside from this lateral inhibition, inhibition may occur in the outer plexiform layer. Brown and Wiesel have reported that cat bipolar cells exhibit off-core regions, and thus fall into the same electrical classification as ganglion cells. The fact that the C-type of S-potential changes sign with wavelength also suggests an inhibiting mechanism. However, neither of these sources is conclusive: it is possible that Brown and Wiesel recorded from ganglion cells rather than bipolars, since no other intracellular recordings purported to be from bipolars have been found in the literature; the S-potentials have been reported under conditions of diffuse illumination, and thus the possibility remains that the change in sign of the C-potential reflects the lateral inhibition of horizontal cells.

Although these recordings only suggest, rather than imply, that there are inhibitory mechanisms other than lateral inhibition, there is no reason to preclude the possibility. Some receptors may (but probably do not) inhibit bipolar cells. There is a possibility that interreceptor inhibition is mediated by the direct connections described in Section II, although it is not clear how or under what conditions this might occur. Intuitively, one would anticipate that cones would inhibit rods as the former are activated by increasing illumination levels. However, as only a small percentage of rods could be inhibited in this manner because of the large rod-to-cone ratio, the effectiveness of such a mechanism is questionable.* Furthermore, the rod--cone synapse at the rod, observed in the primate, is indistinguishable from a rod--bipolar synapse, suggesting a rod-to-cone polarization. There are ample rods for a blanket inhibition of cones. However, although extensive interreceptor connections have been reported in the guinea pig, they have been observed only exceedingly rarely in the primate, despite intensive investigation.

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*There are about 15 to 20 rods per cone. Villegas[8] suggests about 10 processes per cone. If half of these tended to inhibit rods, only about 30 percent of the rods would be inhibited. Furthermore, the abundance of rod--cone connections appears to be very much less than this estimate.

The question of rod--cone interaction, and in particular, whether under some conditions rods and cones function simultaneously, is fundamental and unresolved. Most likely, cones are inoperative at low levels of illumination. Whether rods are inoperative at high levels of illumination is not so clearly established. Psychophysical just-noticeable-difference data[16] and electrical data[13-15] from receptors seem to suggest this, but the point remains open.

Turning to the second manifestation of the off-response -- the increased electrical activity following the cessation of illumination -- one finds suggestions that rods may be active in photoptic vision. The positive off-activity might be explained if both excitatory and inhibitory influences were active during stimulation, with the latter decaying more rapidly than the former upon cessation of illumination. This is illustrated in Fig. 15. Core off-responses may persist for a period of the order of 100 msec or more. Typically, a given cell shows the same type of response at low and high levels of illumination. The time course of cone responses is very similar to the time course of stimulation. Rod responses, on the other hand, have been reported to lag behind the stimulus and to exhibit high levels of activity for hundreds of milliseconds after the light is extinguished. The hypothesis that rod activity does mediate off-responses thus becomes attractive. This conjecture is consistent with the implication of Hubel and Wiesel's work that off-cores are absent from the fovea, but this could also be explained by the absence of mop bipolars from the fovea, as noted above.

On the other hand, there are other possible sources of the off-response. It is possible, for example, that the photochemical processes of some receptors are inhibited by illumination and display high levels of activity after inhibition. However, recordings supposedly from single receptors have all been of the same sign. Two other possible sources of the intensified off-response are related to the fundamental question of the source of spontaneous activity. First, some retinal neural elements may be sensitized by activation, and thus may respond more intensely following stimulation of the source of spontaneous activity, whatever it might be. Such an effect might be related to the phenomenon of post-tetanic potention. A second possibility is that the source of spontaneous activity may become more active following illumination.

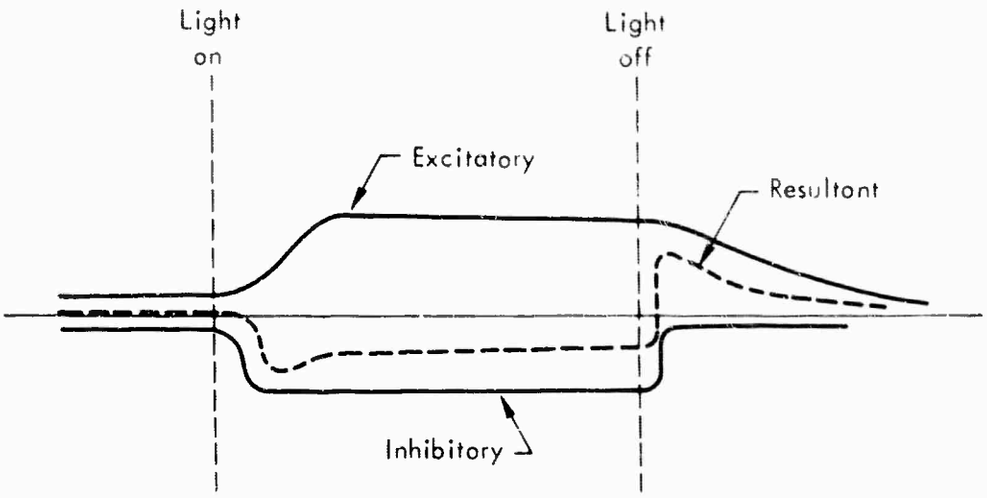


Fig. 15 -- A possible substrate for some off-responses.

The source of spontaneous activity in the retina is a fundamental and unresolved problem. Because of spontaneous activity, inhibiting responses are able to depress resting activity as well as to inhibit excitatory responses to light. Granit suggested in 1955[79] that spontaneous activity originates in receptors. Since then, however, some evidence has indicated that other structures may be responsible.[1] Several investigations of the time course of retinal adaptation have shown a difference between the time course of spontaneous activity and that of photochemical adaptation. Furthermore, spontaneous activity in the lateral geniculate nucleus has been shown to be influenced by the reticular system of the brain stem, as well as by retinal activity. Thus arises the very interesting idea that spontaneous activity may be related to efferent influences from the brain stem. This idea has a certain plausibility, as the activity of that structure has been related to the phenomenon of "attention" or "wakefulness" by many experimental studies.[80] It is not clear, however, at what point these conjectured influences might be first mediated in the retina. As we have seen, efferent fibers have not been traced to their terminals within the retina.

Suppose we return now to Fig. 14 and ask, in view of the foregoing considerations, what might be the underlying basis for the distinction between on- and off-core ganglion cells. Off-core cells tend to exhibit larger core diameters, to have shorter latencies, to exhibit slightly higher rates of spontaneous activity, and are perhaps not present in the fovea. The classification of diffuse ganglion cells into radiate and tufted types is guided by a theoretical prediction of their tendency to respond differentially to excitation (see Section III). This classification is not necessarily related to "on-ness" or "off-ness," which reflects the input.

It is possible that the response-type of the ganglion cell is determined by mop bipolars, and one could postulate that a ganglion cell exhibits an off-type behavior if and only if a mop bipolar synapses upon it. Several facts indicate that this suggestion has some merit. For example, mops are not found in the fovea, and the axo-somatic connection would provide a pathway that could account for the shorter latency of the off-response. On the other hand, the concept is probably not adequate by itself. There is the possibility, discussed above, that off-effects are found prior to the bipolars. Furthermore, a single mop bipolar could not produce a homogeneous field as large as those observed in ganglion cells. (The dendritic spread of a mop is probably less than 100 microns, compared to observed ganglion diameters of up to 600 microns.)

It seems most likely that amacrine cells are quite active in modulating the impulses from the ganglion-cell core. This is indicated by the electronmicroscopic evidence that they join bipolar and ganglion cell processes, and by the observed homogeneity of electrical responses in the core.

Two interesting features of the peripheral annulus of the ganglion cell's receptive field are, first, that it always opposes the core (that is, if the core region tends to excite the ganglion cell then the core tends to inhibit it, and vice versa), and, second, that its effects are

absent in the dark-adapted state. The latter, taken together with Polyak's report that only cones activate the horizontal cells, suggests quite strongly that horizontal cells mediate the opposing periphery, an interpretation that appears to accord with the intracacies of the electrical data. Whether the horizontals effect a synaptic or presynaptic inhibition of bipolar cells cannot be resolved by present histological evidence. It is recalled that Polyak reported that horizontals synapse with rods and cones, whereas Villegas observed horizontal-cell synapses upon bipolar cells. Either possibility would be consistent with its always-opposing effect. This question is treated in more detail in Section V.

A fundamental question concerns the extent of lateral interaction mediated by horizontal cells. The impression is conveyed by the core and opposing-periphery receptive-field organization of ganglion cells that lateral interaction is mediated by horizontal cells connected directly to the direct core pathways. Anatomical data, however, indicate the horizontal cells may interconnect and thus form a lateral network pervading the entire retina.

The neuroelectric data do not seem to be inconsistent with the existence of such a network. In attempting to apply such a concept to receptive field organization of ganglion cells, one must note first that many such inhibitory chains of horizontals would be involved in the receptive field of a single ganglion cell; and second, that the angle between connecting horizontals most likely would be completely random. This idea is illustrated in Fig. 16. Thus, the receptors exciting the "first-order" horizontals should indeed fall in an annulus around the receptive field center. On the other hand, the receptors exciting nth-order horizontals could lie anywhere within a circle with radius of n horizontal cell lengths. It is clear that such organization would not be clearly revealed by the experimental investigations of ganglion receptive-field organization. Furthermore, there are exceptions to the core-opposing-periphery organization typical of ganglion cells. Perhaps the most striking with respect to the idea of an inhibitory chain of horizontal cells is the finding of McIlwain[81] that the firing response in a cat ganglion cell may be influenced by a stimulus located some 3 mm from the receptive field center.

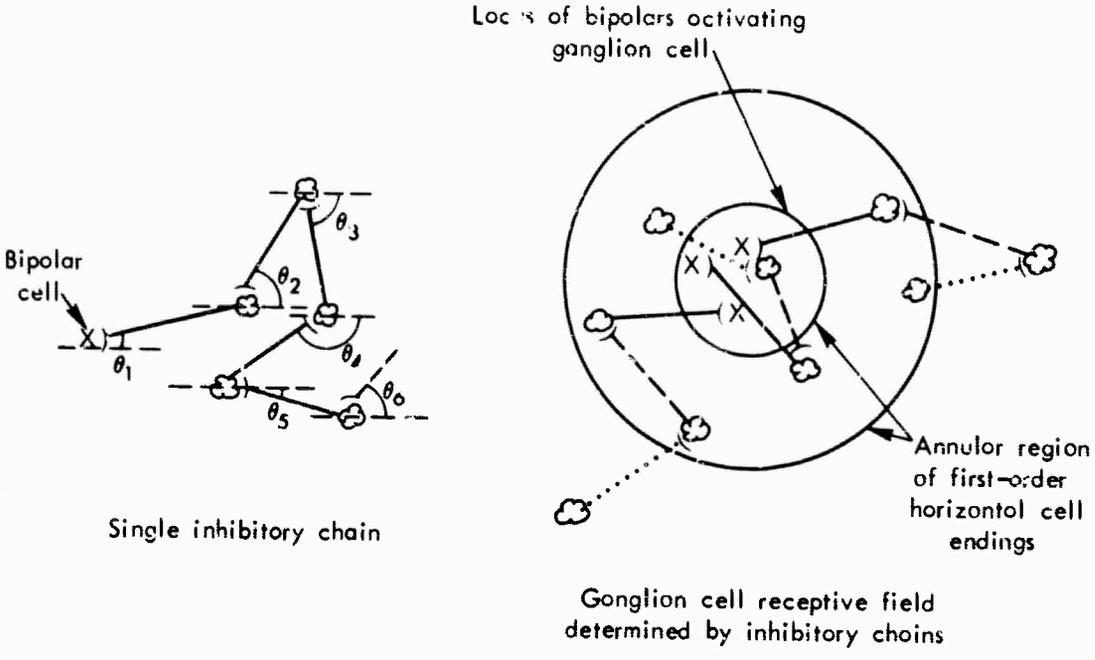


Fig. 16 -- The inhibitory chain hypothesis.

Post-stimulus histograms of ganglion-cell spike trains show that the probability of firing waxes and wanes periodically with a preferred interval (for cat ganglion cells) of about 20 msec.[1,82] Clearly such behavior can be accounted for on the basis of an inhibitory chain, and we have, in fact, found such behavior in a pilot model of a single inhibitory chain.

B. HYPOTHETICAL ORGANIZATION SCHEMA

The following assumptions comprise a reasonable working schema of neural organization in the retina:

1. The following classes of cells occur in the retina: rods and three classes of cones (distinguished by spectral sensitivity); midget, brush,* and mop bipolars; midget, radiate, and tufted ganglion cells; horizontal cells and amacrine cells.

*Includes Polyak's flattop.

2. Interconnection patterns are primarily those described by Polyak, except that horizontal cells synapse with bipolars and the amacrines connect as indicated by recent electron-microscopic investigations.
3. Receptors respond to illumination by releasing a chemical transmitter whose quantity is proportional to the intensity of the illumination and exhibits, say, a Gaussian dependence on its wavelength.
4. Horizontal and amacrine cells exhibit a graded electrotonic activity (that is, do not produce spike potentials), whereas bipolar and ganglion cells behave like the "standard motoneuron."
5. All junctions are mediated by excitatory synapses (except for horizontal→bipolar and mop bipolar→ganglion, which are synaptic inhibitory, and perhaps amacrines, whose characteristics are in need of further study).

The connection patterns for ganglion-cell core regions as determined by this schema are illustrated in Figs. 17 and 18. The lateral connections of horizontal and amacrine cells are superimposed upon these "direct" connections.

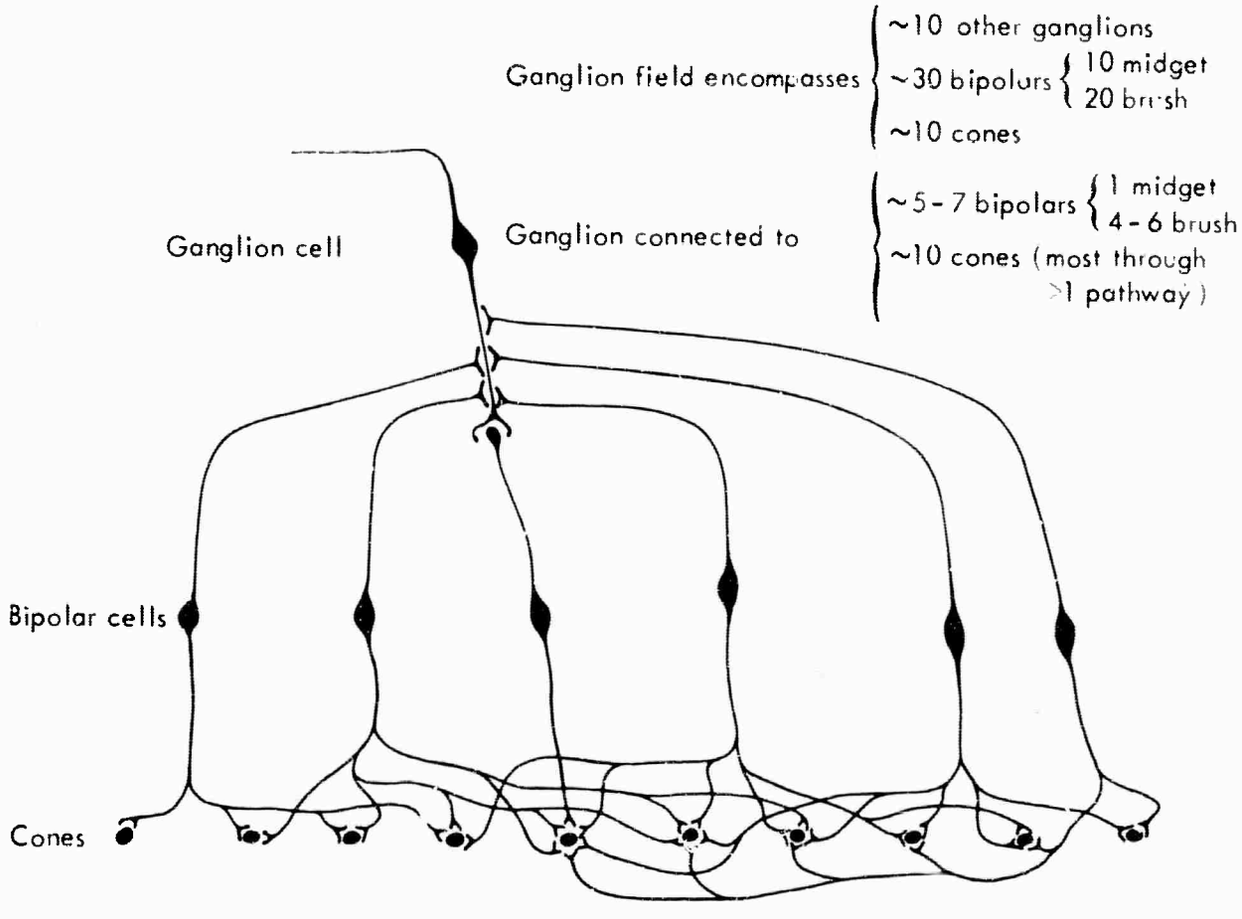
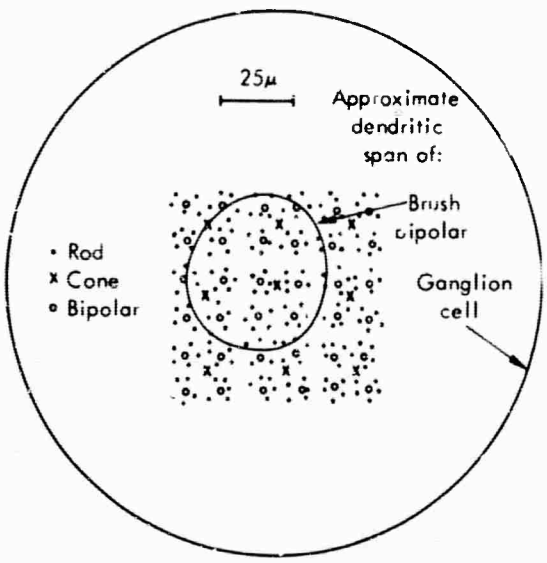


Fig. 17 -- Hypothetical foveal unit; each bipolar (except midget) connects to 1 or 2 other ganglions; each cone is connected to about 1 midget and 12 brushes.

Ganglion field encomposses
- ~100 - 600 cones
- ~2000 - 12000 rods
- ~400 - 2400 bipolars
  - 50 - 300 midgets
  - 10 - 100 mops
  - 320 - 2000 brushes
- ~40 - 250 other ganglion

Ganglion connected to
- ~1 mop
  - ~6 cones
  - ~10 - 60 rods
- ~20 brushes
  - ~60 cones
  - ~60 - 100 rods
- ~3 midgets
  - ~3 cones
  - ~0 rods
- ~50 cones
- ~100 rods



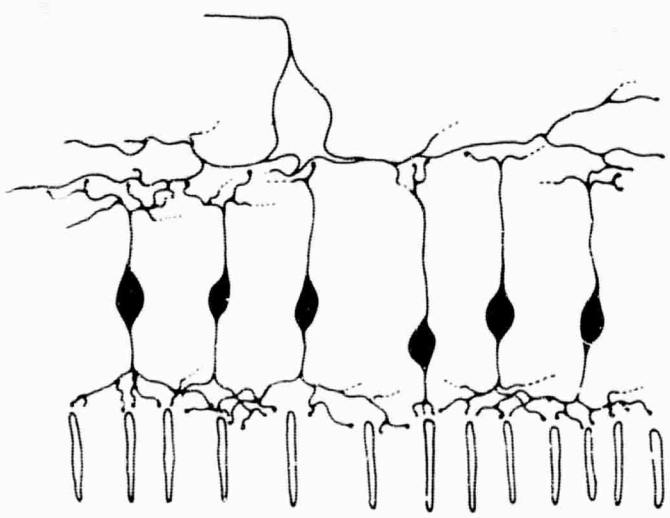


Fig. 18 -- Hypothetical peripheral connections.

V. GENERATOR THEORY AND PROCESSES OF THE OUTER PLEXIFORM LAYER

Neglecting possible interreceptor interaction and efferent influence, retinal processing may be envisaged in two stages: (1) a transfer from the receptors through the outer plexiform layer to the bipolar layer, and (2) a transfer from bipolar cells through the inner plexiform layer to the ganglion-cell layer. This section presents a theoretical schema for the processes of the first stage, and discusses its relation to pertinent electrical recordings and to the encoding of stimulus intensity. In particular, it is shown that the generator theory of nerve-cell function, applied within the framework of retinal interconnection patterns, seems to provide an adequate neurophysiological basis for the properties of retinal S-potentials and for the subjective ability to discriminate differences in stimulus intensity. The present discussion is based upon quantitative analyses that are partly described in Ref. 54.

A. GENERATOR THEORY AND RETINAL S-POTENTIALS

Suppose that receptors activate bipolar and horizontal cells by a typical synaptic mechanism; that is, a chemical transmitter changes the permeability of the subsynaptic membrane, and the resulting ionic process is characterized by an equilibrium potential. Suppose that (1) all receptor synapses are excitatory; (2) the permeability change endures throughout illumination and is proportional to its intensity; and (3) horizontal cells and the dendritic regions of bipolar cells exhibit linear membranes except at synapses. Thus, in this schema horizontal cells do not produce electrical spikes, but exhibit graded electrical activity throughout their operating range.

It is easy to show[54] that a single synapse of this type mediates in the bipolar or horizontal cell an electric response whose amplitude depends on intensity according to:

$$\frac{E}{E^*} = \frac{I}{1 + I} \qquad (2)$$

where E is the potential, E^* the synaptic equilibrium potential, and I the stimulus intensity. A salient feature of this relation, which is shown in Fig. 19, is that the response is approximately proportional to the logarithm of stimulus intensity, but only for a range of about two log units. This characteristic is independent of the sensitivity of the receptor mechanism; for example, changing I to kI in Eq. (2) merely shifts the curve rigidly by a distance k along the abscissa. We have shown[54] that this relation holds approximately for a dendritic branching pattern representative of a typical bipolar or horizontal cell.

This mechanism accounts for the linear relation observed between stimulus intensity and receptor response (see Section III).* Furthermore, together with the supposition that horizontal cells effect a synaptic inhibition upon bipolar cells, it does provide a framework for understanding the electrical interaction occurring in the first retinal stage.

The electrical data most pertinent in the outer plexiform layer are the S-potentials (see Section [illegible]). These recordings are quite consistent with the present schema under the assumption that they are extracellular recordings in or around the neuropile. We suppose (see Fig. 20) that the L-units reflect activity external to the level at which the horizontal cells inhibit bipolars and that the C-units reflect activity near or internal to these junctions. This is consistent with the experimentalists' report[57,58] that the C-potentials are recorded near the bipolar nuclei and the L-units near the horizontal cells.

Both types of potentials exhibit precisely the dependence upon stimulus intensity predicted by the present theory; that is, the curves are approximately linear superpositions of relations of the form of Eq. (2); there are slight deviations which are quite consistent with characteristics of interaction among different synapses.

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*The suggestion is sometimes made that logarithmic-like intensity encoding is mediated by receptor mechanisms. However, the present theory is more easily applied to other sensory modes; this is not possible for a theory that relies heavily upon properties of highly specialized photoreceptors.

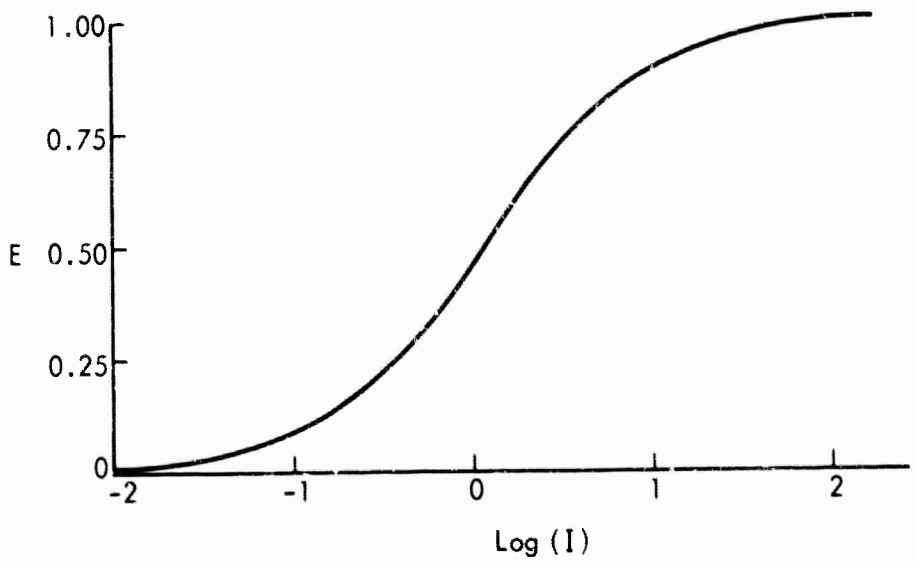

Fig. 19 -- Response-intensity relation from the generator theory.

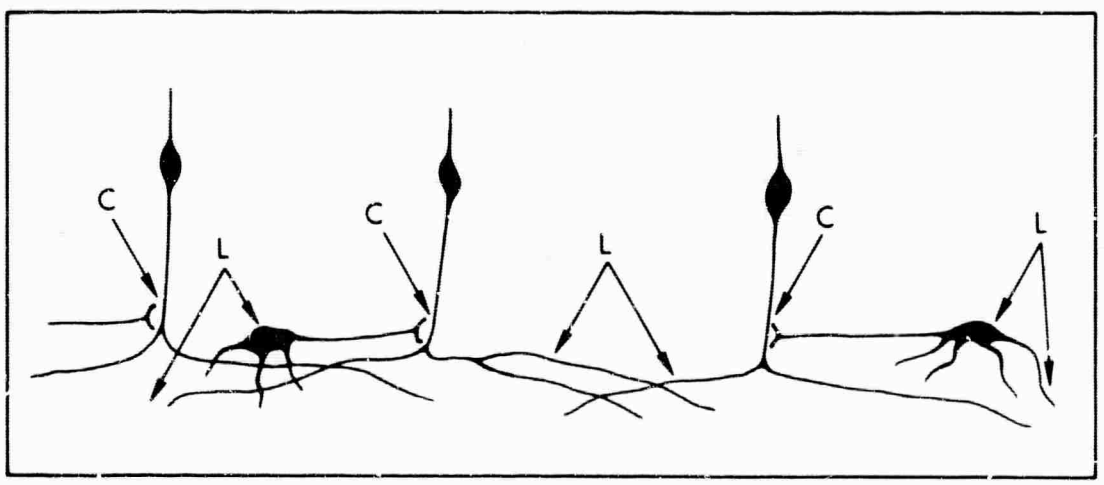

Fig. 20 -- Hypothetical scheme for the origin of S-potentials (L-units reflect only direct excitation, while C-units incorporate inhibition by horizontal cells).

The fact that S-potentials are predominantly hyperpolarizations (which would be inhibitory were they intracellular) has caused some consternation. However, it is very plausible that extracellular recordings in the retinal neuropile could approach the 25- to 30-mv amplitudes of some S-potentials. It should be noted that the schema being presented here is concerned with relatively large-amplitude depolarizations. The theoretical saturation potential in the absence of an inhibitory process is the equilibrium potential of the excitatory synaptic process; that is, 70 mv. Typically, extracellular responses are much smaller (less than about 1 mv) for an intracellular response of this magnitude.(83) However, the extremely high density of fibers in the neuropile must increase the external electrical resistance. Furthermore, most experimental reports describing properties of S-potentials rather strongly suggest an extracellular origin. For example, Naka and Rushton state:

> When a nerve or muscle is impaled, there is usually a sharp change of potential at the moment of penetration, and not much change with electrode position before or after. The penetration of the S-unit is often not such a definite step; the change was frequently a rather gradual transition and the response to a fixed light flash seemed to depend upon the exact position of the electrode tip.(57)

Finally, it is intuitively more satisfactory to regard the predominant response of receptors as excitatory rather than inhibitory, which would be the case if the S-potentials were intracellular.

In this schema, then, the L-potentials reflect only excitatory responses, for all wavelengths of white and colored light. The C-potentials, on the other hand, are excitatory (negative extracellular recording) when the direct (core) influence is predominant, and inhibitory (positive extracellular recording) when the inhibiting effect of the horizontal cell is predominant. It is recalled (see Section III) that C-potentials tend to exhibit hyperpolarizing responses at short wavelengths and depolarizing effects at longer wavelengths. This is consistent with the idea that only cones activate horizontals and the supposition that both rods and cones are active on the bipolars. Were this the case, the longer wavelengths would tend to emphasize the

influence of horizontal cells over that of the direct core. Another experimental observation tends to corroborate this interpretation of the association of long wavelengths with excitation responses. Svaetichin[84] has found off-responses only in C-potentials and only when the stimulus was either white light or monochromatic light near the neutral point. No off-responses were found in L-potentials. Since the activity of cones appears to follow the time course of stimulation very closely, the explanation that the off-responses reflect the disinhibition of core rods by peripheral cones seems very attractive.

Polyak has reported contrary to the present interpretation, that the output processes of horizontals terminate on receptors. However, most electronmicroscopic observation has been unable to follow horizontals to their terminations, and Villegas has reported observing horizontal-to-bipolar connections.

Several factors have led us to assume that horizontals effect a synaptic inhibition on bipolar cells. For example, if horizontals connected with receptors it is most likely that their influence would be mediated by presynaptic inhibition. It is very difficult to understand how a presynaptic mechanism could account for a depression of activity below the resting level, since presynaptic mechanisms typically merely modulate the release rate of the presynaptic transmitter. This difficulty could be resolved only if receptors were the source of spontaneous activity, and current evidence argues against this (see Part B).

Also, the relative amplitudes of the hyperpolarizing and depolarizing portions of the C-potentials match very well the relative equilibrium potentials of the excitatory and inhibitory synaptic mechanisms. The hyperpolarizing (short-wavelength) portion of the response theoretically exhibits a saturation potential of 70 mv, whereas that of the depolarizing (long-wavelength) response is about -.0 mv.[66] Since the recordings are extracellular their absolute magnitude is smaller, but their ratio should be about the same.

The interpretation presented here, then, is truly a "generator" theory, in the sense that spike potentials are not included. Spikes are assumed to be elicited first in bipolar cells, and thus interaction

at the second retinal stage is somewhat different from that in the outer plexiform layer. We suggest that logarithmic-like intensity encoding reflects the properties of this theory of the generating potential, and although highly nonlinear neural processes occur in the second retinal stage and higher centers, reflections of these mechanisms may be observed in psychophysical studies. Before turning to this suggestion, however, we consider some tests to which the above ideas are subject.

Electrical activity recorded in various stages of the visual system[1] is consistent with the ideas presented above. Spike activity has been reported near the level of the bipolar nuclei, but not distal to it; indeed, all recordings distal to that level exhibit only graded activity (see Section III). Furthermore, the observed relations between stimulus intensity and the amplitudes of various electrical responses are quite consistent with those implied by the generator mechanism. It must be borne in mind that Eq. (2) is exactly applicable only to the artificial case of a single active synapse, and that even in individual bipolar and horizontal cells some deviations from theory arise because of synaptic interaction.[54] Furthermore, the relation of Eq. (2) is certainly modified by mechanisms in the second retinal stage. Thus, in view of the expected counteraction of excitation and inhibition through numerous cross-connecting fibers in the retina, one expects to find in ganglion cells and at higher levels only well-masked reflections of the fundamental relation.

The trends of electrical activity agree somewhat better with Eq. (2) than might be expected, considering the many facets of retinal integration that the equation does not explicitly include. For example, Eq. (2) should be best satisfied under conditions of dark adaptation and core illumination only. (Both these conditions eliminate the lateral inhibition of horizontal cells.) Figure 21 shows two types of recording from the dark-adapted cat eye, which match the theoretical curve extremely well. The first represents the amplitude of the b-wave of the ERG[85] (which this writer interprets as the gross response of the neuropile in the outer plexiform layer), and the second measures spike frequency in a ganglion cell.[86]

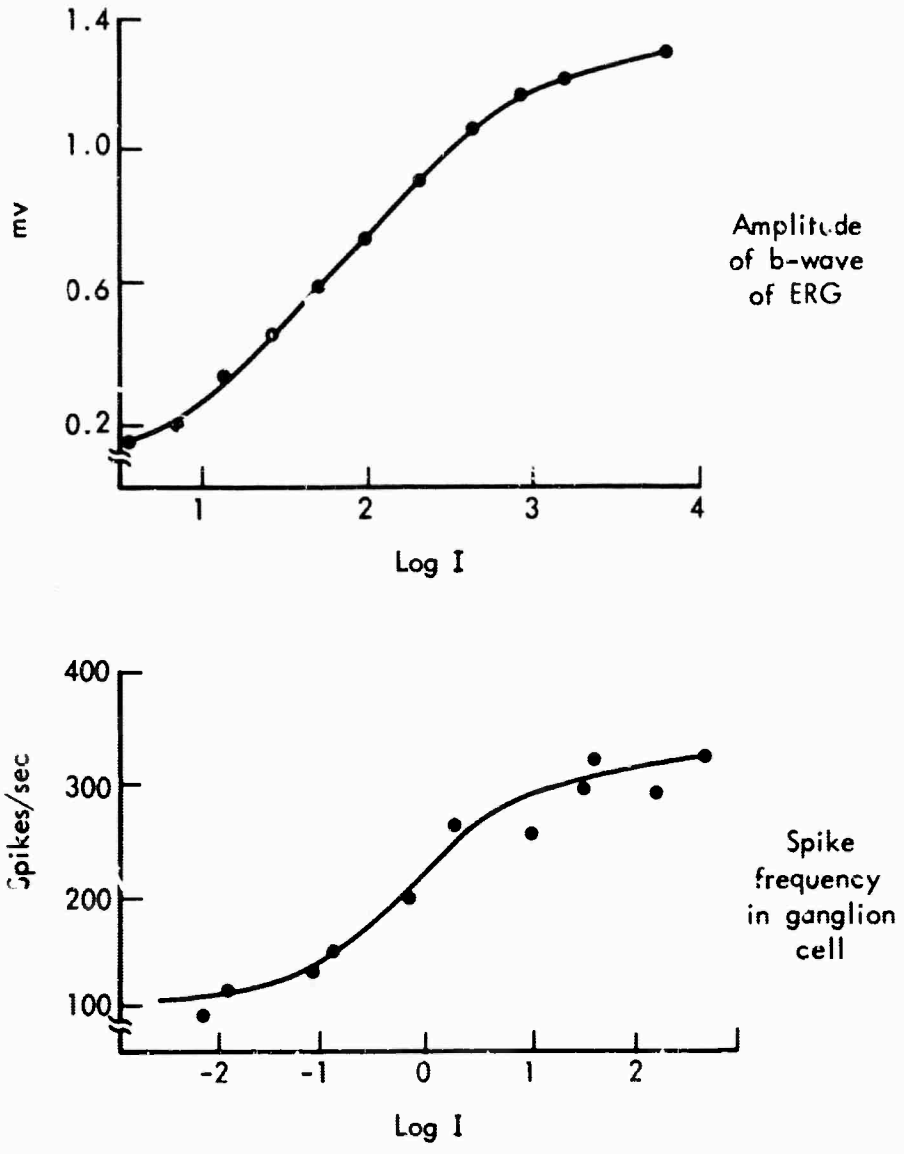

Fig. 21 -- Experimental response-intensity relations in dark-adapted cat eye.

Experimental observations of retinal electrical activity generally do not satisfy Eq. (2) as well as do those two cases. However, the spike frequency of ganglion cells has been repeatedly repor to exhibit a sigmoid dependenc upon the logarithm of light intensity.(1) Slopes vary greatly and the amplitude sometimes tends to diminish at very high intensities, but the general trend clearly reflects a logarithmic-like dependence over about 1.5 to 3 log units.

The present interpretation of the S-potential is subject to direct experimental test. First, the position that C-potentials reflect an interaction between direct influence and influences mediated by horizontal cells could be easily tested with small-diameter stimulation. In particular, no C-potentials should be observable if the stimulus is a small-diameter light. Second, the receptive fields of bipolar cells should consist of a core and opposing periphery, but all core regions should b excitatory.

Should the general structure of the present position be confirmed, a more fine-grained prediction would be testable: the L-potentials should exhibit different amplitudes of response to different wavelengths of light. However, since only excitatory synapses are effective, the saturation potential for white light and monochromatic light of any wavelength should be about the same. (A small variation could be accounted for if cones with different spectral properties lay at different distances from the electrode.) On the other hand, the saturation potential of the C-potentials should vary systematically with wavelength, depending on the relative strengths of activation of the direct and peripheral influences. Saturation potential should thus vary monotonically from somewhat less than 70 mv when the core influence is maximized to somewhat more than about -10 mv when the peripheral influence is maximized.

B. GENERATOR THEORY AND THE ENCODING OF STIMULUS INTENSITY

Several factors suggest that the subjective sensation of brightness is related to the frequency of firing in ganglion cells. For example, the time-course of brightness sensation,(87) shown in Fig. 22,

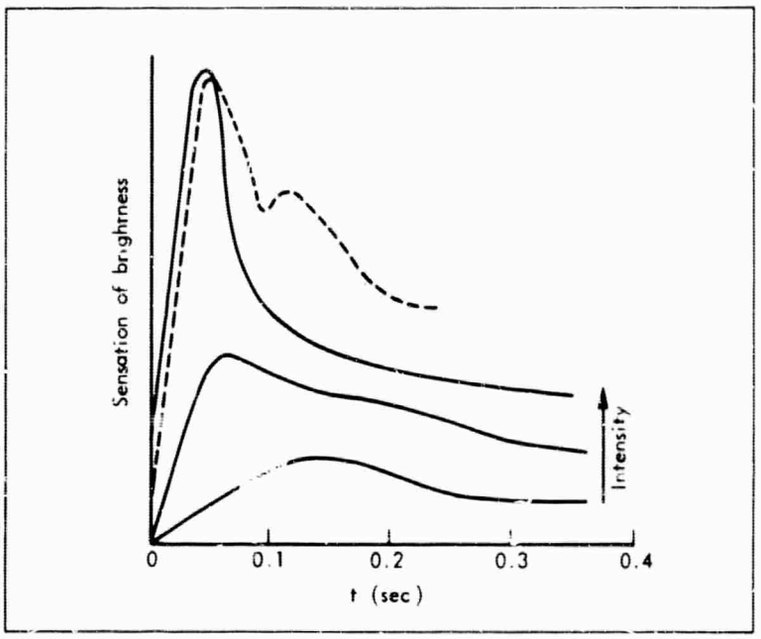

Fig. 22 -- The time course of brightness.

corresponds to the time-course of frequency in ganglion cells.[1] (The generator theory provides a possible explanation of this depression,[54] but other mechanisms may be involved.) Furthermore, both the sensation of brightness and the firing frequency of ganglion cells are logarithmically related to stimulus intensity.

The logarithmic-like dependence of subjective brightness on stimulus intensity was recognized over a century ago.[88] Fechner formalized the observation on the basis of a metaphysical theory with the statement that sensation is proportional to the logarithm of stimulus intensity. The Weber--Fechner law, as Fechner's formulation has since been known, has proved sufficiently accurate to have remained in textbooks and in the minds of researchers for over 100 years; at the same time, however, its inadequacies and limitations have been the source of continuing polemics. Stevens, the most recent of the many critics who have dealt harshly with Fechner's generalization, claims that power-law curves fit response intensity data for many sensory modes.[89]

Figure 23 shows just-noticeable-difference data for human vision for a dark surround and an illuminated surround.[16] For a dark surround the jnd curves exhibit an approximately flat trough for only about one log unit. In this case, where the surround is inactive, the generator theory as expressed here predicts that electrical activity in single units will most closely follow Eq. (2). From Eq. (2) we obtain

$$\frac{dI}{I} = \left(\frac{1}{I} + 2 + I\right)dE \qquad (3)$$

which approximates the change in electrical activity, dE, associated with a change in stimulus intensity, dI. Figure 23b shows dI/I versus I from Eq. (3) for constant dE. If the comparison shown in Fig. 23 is meaningful, and it seems most reasonable to assume that it is, it suggests that the subjective jnd in stimulus brightness corresponds to a constant increment of electrical activity.

When the surround is illuminated also, the width of the trough in the subjective jnd curve increases; that is, the intensity range over which an extrapolated sensation of brightness is proportional to the logarithm of stimulus intensity is increased. This is precisely what we would anticipate on the basis of the lateral inhibition discussed above. However, it must also be borne in mind that more ganglion cells are affected by stimulation in this case than when only the core is illuminated. Thus, the increased probability of a wider spread in sensitivity among the ganglion cells (that is, the intensity level at which the cell becomes active) may also play a part in this flattening.

A power law with exponent 1/3, which Stevens finds for vision, yields a straight line with slope -1/3 on a log-log plot of dI/I versus I. The absence of a flat trough in this relation corresponds to the failure of a power law to flatten at high intensity levels. Figure 23a shows, first, that the 1/3 power-law does approximate the jnd data, but, second, that the intensity range for which Stevens presents data does not encompass the interval where the flattening occurs in the jnd data.

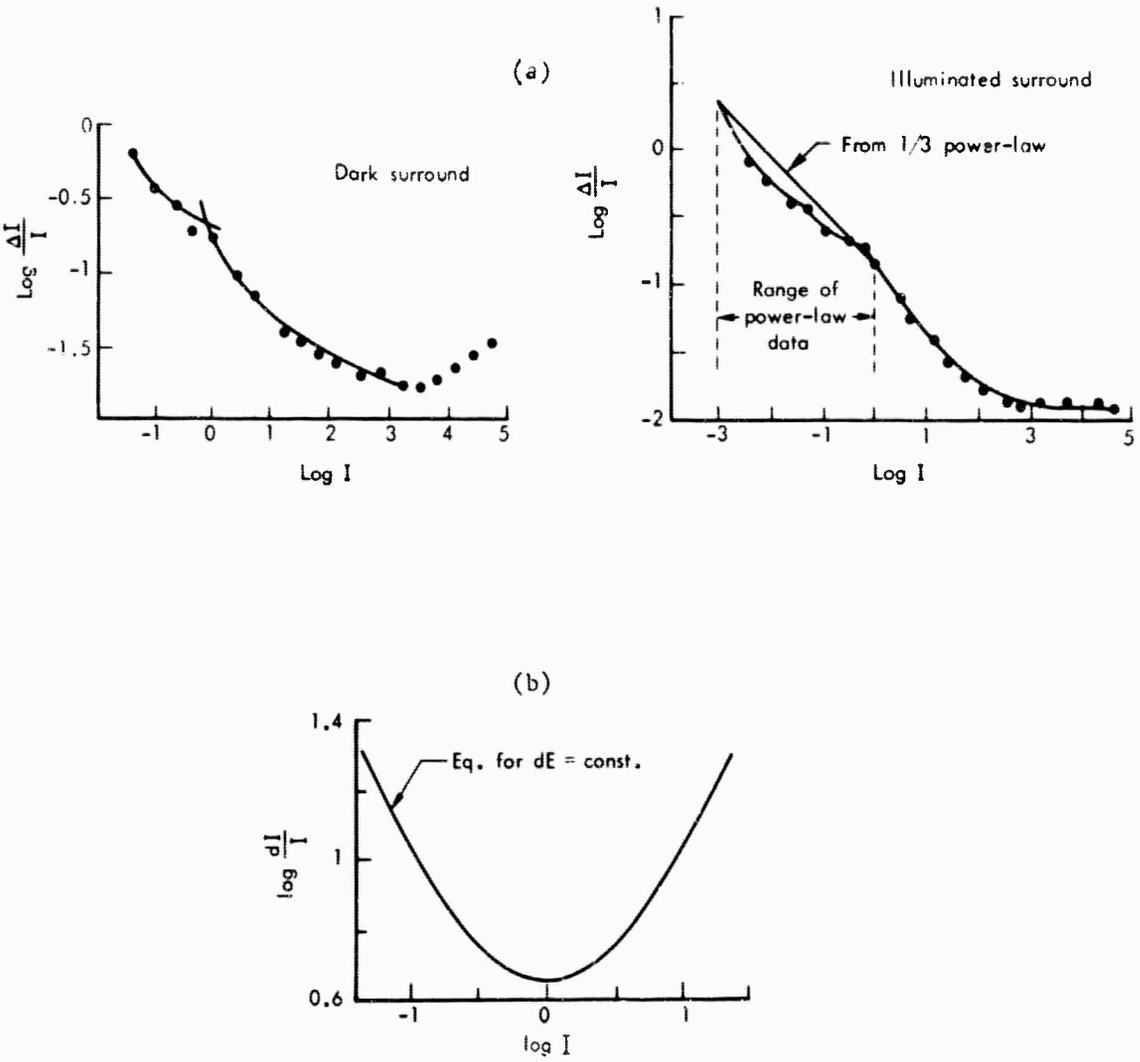

Fig. 23 -- The just noticeable difference.

The subjective sensation of brightness most certainly depends on the combined activity of a large number of cells. This fact must be considered before the relation presented here is applied to details of psychophysical data.

It is clear that the interpretation of intensity encoding is in a primitive stage of development. It should be equally clear that the most meaningful approach to this and related problems consists of linking psychophysical and electrical data to the underlying neurophysiological mechanisms. Only on such a basis will we eventually be able to speak with confidence of the law (or laws) of intensity encoding. In particular, the attempts to elevate a power-law relationship to the status of a law on the basis of arbitrarily matching curves to datapoints must be viewed with considerable skepticism.

VI. CONCLUDING REMARKS

This work has attempted to outline the neuroanatomical, neuroelectrical, and neurophysiological findings relevant to an understanding of retinal organization. In addition, some tentative functional hypotheses have been presented and an attempt made to tie together anatomical, electrical, physiological, and behavioral information relating to the encoding of stimulus intensity.

The information presented here may be viewed from any of several orientations, and by the same token, progress from here may take any of several directions, depending upon the motivations, goals, and orientation of the investigator. For example, one might be interested in an overall view of the neural behavior of the retina, per se. That is, one might want to answer the question "What are the patterns of interconnection and the mechanisms that underlie the diverse electrical responses observed in the retina?" Again, one might be interested in understanding the functional role of the retina in a given phenomenon of visual perception. Or one may regard the study of neural behavior in the retina as of interest primarily because it serves as a special case from which a more general conceptual framework may be developed. From this orientation, one might hope to acquire from a study of the retina an intimacy with modes of neural integrative mechanisms and perhaps with a descriptive methodology which may be applicable to neural systems in general.

It should be clear from the preceding sections that several questions need to be resolved before a satisfactory overview of retinal organization is attained. For example, we need to know the source and mechanisms of spontaneous activity, the extent and characteristics of efferent influence, and the functional properties of amacrine cells; we need to know more about the physiological processes of adaptation and the extent and characteristics of functional overlap and interaction between rods and cones. Furthermore, it is quite possible that as-yet-undiscovered details of interconnection patterns may be crucial.

On the other hand, it is not clear how much more detailed experiment is required, and pointed theoretical analyses may very well help

to resolve some of these questions. An investigator with this orientation would wish to stay abreast of appropriate experimental findings while devising and testing functional hypotheses. One might, in fact, be able to progress profitably with analytical methods alone, eschewing the laboratory perhaps indefinitely, since electrical data are very numerous and detailed.

The value of such an approach is not that one might build a model whose behavior approximates some features of retinal function; rather one would be forced to come to grips with the mechanisms that determine the observed activity, and thereby gain insight into retinal function not directly clear from electrical data.

Whether one chooses the organization schema presented in Section IV or another, a distinction between foveal and peripheral units is evident. Both are of interest from a theoretical point of view; the foveal unit, in particular, is relatively simple and well defined, and thus invites theoretical analysis despite the lack of appropriate electrical data from the fovea.

The investigator interested in the functional role of the retina in a given perceptual phenomenon need not necessarily be concerned with all the questions confronting the investigator interested in retinal organization per se. Unfortunately, however, it is not clear a priori how much detail should be considered or which characteristics may be safely ignored. Furthermore, one must be aware that the retina comprises only a small part of the neural apparatus involved in visual perception. The discussion of intensity encoding in Section IV, for example, indicates both the possible rewards and the limitations of such endeavours. In any case, the investigator interested in retinal function from this point of view must sooner or later consider higher structures as well.

A topic for which neural analysis seems presently very propitious is color vision. The S-potentials and spike recordings in ganglion and lateral geniculate cells provide ample guidelines for constructive theoretical work. Indeed, one might hope to see in the not-too-distant future a satisfactory resolution of some century-old questions about color vision. For example, theories of color-mixing obviously await

an appropriate neurophysiological mechanics; and the S-potentials have provided the first stages for a synthesis of the Young-Helmholtz three-color theory and Hering's opponent-process theory.

In either of these two orientations, one eventually encounters two questions of primary concern to the investigator with the last-mentioned orientation. First, how do we adequately describe the behavior of a given collection of nerve cells; and second, what measures of their activity are appropriate for our purposes?

In all probability the answers to these questions will in the long run most increase our general understanding of both neural and retinal function.

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REFERENCES

1. MacGregor, R. J., Pulse Trains in Lateral Geniculate and Retinal Ganglion Nerve Cells, The RAND Corporation, RM-4870-ARPA, November 1966.

2. Dogiel, A. S., "Ueber die nervösen Elemente in der Retina des Menschen," Zweite Mitth. Arch. f. mikrosk. Anat., Vol. 40, 1892, pp. 29-38.

3. Ramón y Cajal, S., Histologie Du Systeme Nerveux, Vol. II, Instituto Ramón y Cajal, Madrid, 1955.

4. Polyak, S., The Vertebrate Visual System, The University of Chicago Press, 1957.

5. Walls, G. L., The Vertebrate Eye and Its Adaptive Radiation, Hafner Publishing Co., New York, 1963 (2nd ed.).

6. Missoten, L., "Étude des Batonnets de la rétine Humaine au Microscope Électronique," Ophthalmologica, Basel, Vol. 140, 1960, pp. 200-214.

7. Wolken, J. J., "Studies in Photoreceptor Structures," Ann. N. Y. Acad. Sci., Vol. 74, 1958, pp. 164-181.

8. Villegas, G. M., "Ultrastructure of the Human Retina," J. Anatomy, Vol. 98, 1964, pp. 501-513.

9. Villegas, G. M., "Comparative Ultrastructure of the Retina in Fish, Monkey and Man," in The Visual System: Neurophysiology and Psychophysics, R. Jung and H. Kornhuber (eds.), Springer-Verlag, Berlin, 1961.

10. Dartnall, H. J. A., "The Photobiology of Visual Processes," Part II in The Eye, Vol. 2, H. Davson (ed.), Academic Press, New York, 1962.

11. Brown, P. K., and G. Wald, "Visual Pigements in Single Rods and Cones of the Human Retina," Science, Vol. 144, 1964, pp. 45-52.

12. Brown, P. K., and G. Wald, "Visual Pigments in Human and Monkey Retinas," Nature, Vol. 200, 1963, pp. 37-43.

13. Brown, K. T., and K. Watanabe, "Rod Receptor Potentials from the Retina of the Night Monkey," Nature, Vol. 196, 1962, London, pp. 547-550.

14. Brown, K. T., and K. Watanabe, "Isolation and Identification of Receptor Potentials from the Pure Cone Fovea of the Monkey Retina," Nature, Vol. 193, 1962, pp. 958-960.

15. Fatchchanda, R., M. Laufer, and G. Svaetichin, "Retinal Receptor Potentials and Their Linear Relationship to Light Intensity," Science, Vol. 137, 1962, pp. 666-667.

16. Pirenne, M. H., "Limina' Brightness Increments," Chapter 8 in The Eye, Vol. 2, H. Davson (ed.), Academic Press, New York, 1962.

17. Sneppard, J. J., A Critical Review of the Experimental Foundation of Human Color Perception, The RAND Corporation, RM-4196-APPA, 1966.

18. Gallego, A., "Connexions Tranversales au Niveau des Couches Plexiformes de la Rétine," Actualités neurophysiol., Vol. 5, 1965, pp. 5-28.

19. Ramón y Cajal, S., "La Rétine des Vertébrés," La cellule, Vol. 9, 1893, pp. 119-246.

20. deTesta, A. J., "Morphological Studies on the Horizontal and Amacrine Cells of the Teleost Retina," Vision Res., Vol. 6, 1966, pp. 51-60.

21 Villegas, G. M., "Electron Microscopic Study of the Vertebrate Retina," J. Gen. Physiol., Vol. 43, 1960, Suppl. 15-43, pp. 15-21.

22. Svaetichin, G., et al., "Nervous Function Based on Interactions Between Neuronal and Nonneuronal Elements," in Biology of Neuroglia, Vol. 15, E. D. P. deRobertis and R. Carrea (eds.), Elsevier, Amsterdam, 1964.

23. Missoten, M., "L'ultra Structure de Cellules Horizontales Externes de la Retine Humaine," Bull. Soc. Belge Ophthal., Vol. 128, 1961, pp. 207-214.

24. Brown, J. E., and D. Major, "Cat Retinal Ganglion Cell Dendritic Fields," Exp. Neurol., Vol. 15, 1966, pp. 70-79.

25. Dowling, J. E., and B. B. Boycott, "Organization of Primate Retina: Fine Structure of the Inner Plexiform Layer," Cold Spr. Harb. Symp. Quant. Biol., Vol. 30, 1965, pp. 393-402.

26. VanBuren, J. M., The Ganglion Cell Layer, Charles C. Thomas, Springfield, Illinois, 1963.

27. Stone, J., "A Quantitative Analysis of the Distribution of Ganglion Cells in the Cat's Retina," J. Comp. Neurol., Vol. 124, 1965, pp. 337-352.

28. Bishop, P., W. Kozak, and G. Vakkur, "Some Quantitative Aspects of the Cat's Ey Axis and Plane of Reference, Visual Field Coordinates and Optics," J. Physiol., Vol. 163, 1962, pp. 466-502.

29. Rushton, W. A. H., "Giant Ganglion Cells in the Cat's Retina," J. Physiol., Vol. 11, 1950, pp. 26-27.

30. Brown, J. E., and J. A. Rojas, "Rat Retinal Ganglion Cells: Receptive Field Organization and Maintained Activity," J. Neurophysiol., Vol. 28, 1965, pp. 1073-1091.

31. Brown, J. E., "Dendritic Fields of Retinal Ganglion Cells of the Rat," J. Neurophysiol., Vol. 28, 1965, pp. 1091-1101.

32. Dowling, J. E., in Proceedings of Technical Meeting Inaugurating the Jules Stein Eye Institute, November 1966, University of California, Los Angeles (in press).

33. Bishop, P. O., O. Jeremy, and J. W. Lance, "The Optic Nerve Properties of a Central Tract," J Physiol., Vol. 121, 1953, pp. 415-432.

34. Chang, H. T., "Fiber Groups in Primary Optic Pathway of Cat," J. Neurophysiol., Vol. 19, 1956, pp. 224-231.

35. Bishop, G. H., and M. H. Clare, "Organization and Distribution of Fibers in the Optic Nerve of the Cat," J. Comp. Neurol., Vol. 103, 1955, pp. 269-304.

36. Osterberg, G. A., "Topography of the Layer of Rods and Cones in the Human Retina," Acta. Ophthalmol., Suppl. VI, 1935.

37. Vilter, V., "Recherches Biométriques sur l'Organisation Synaptique de la Rétine Humaine," Société de Biol., 1949, pp. 830-832.

38. Missoten, L., "Étude des Synapses de la Rétine Humaine au Microscope Électronique," European Regional Conference on Electron Microscopy, Vol. 2, A. L. Houwink and B J. Spit (eds.), Delft, 1960.

39. Yamada, E., K. Tokuyasu, and S. Iwaki, "The Fine Structure of the Retina Studied with Electron Microscope. III the Human Retina," J. Kurume Medical Assoc., Vol. 21, 1958, pp. 1979-2027.

40. Sjöstrand, F. S., "The Synaptology of the Retina," in Color Vision, CIBA Symp., A. V. S. deReuck and J. Knight (eds.), Little, Brown and Co., Boston, 1965, pp. 110-151.

41. Ladman, A. J., "The Fine Structure of the Rod-Bipolar Synapse in the Retina of the Albino Rat," J. Biophys. Biochem. Cytol., Vol. 4, 1958, pp. 459-466.

42. Pedler, C., "Rods and Cones - A Fresh Approach," in CIBA Foundation Symposium on Color Vision, A. V. S. deReuck and J. Knight (eds.), Little, Brown and Co., Boston, 1965.

43. Kidd, M., "Electron Microscopy of the Inner Plexiform Layer of the Retina in the Cat and Pigeon," J. Anatomy, Vol. 96, pp. 179-187.

44. Allan, R. A., in Proceedings of Technical Meeting Inaugurating the Jules Stein Eye Institute, November 1966, University of California, Los Angeles (in press).

45. Eccles, J. C. (ed.), Brain and Conscious Experience, Springer-Verlag, New York, 1966.

46. Arey, L. B., and M. Gore, "The Numerical Relation Between the Ganglion Cells of the Retina and the Fibers of the Optic Nerve of the Dog," J. Comp. Neurol., Vol. 77, 1942, pp. 609-619.

47. Bruesch, S. R., and L. B. Arey, "The Number of Myelinated and Unmyelinated Fibers in the Optic Nerve of Vertebrates," J. Comp. Neurol., Vol. 77, 1942, pp. 631-665.

48. Maturana, H. R., "The Fine Anatomy of the Optic Nerve in Anuransan Electron Microscopic Study," J. Biophys. Cytol., Vol. 7, 1960, pp. 107-120.

49. Mendell, L. M., and P. D. Wall, "Presynaptic Hyperpolarization: A Role for Fine Efferent Fibers," J. Physiol., Vol. 172, 1964, pp. 274-294.

50. Wolter, J. R., and R. R. Knoblich, "Pathway of Centrifugal Fibres in the Human Optic Nerve, Chiasm, and Tract," Brit. J. Ophthal., Vol. 49, 1965, pp. 246-250.

51. Cowan, W. M., and T. P. S. Powell, "Centrifugal Fibres in the Avian Visual System," Proc. Roy. Soc. B., Vol. 158, 1963, pp. 232-252.

52. Brooke, R. N. L., S. de C. Downer, and T. P. S. Powell, "Centrifugal Fibers to the Retina in the Monkey and Cat," Nature, Vol. 207, 1965, pp. 1365-1367.

53. MacGregor, R. J., A Digital-Computer Model of Spike Elicitation by Postsynaptic Potentials in Single Nerve Cells, The RAND Corporation, RM-4877-ARPA, September 1966.

54. MacGregor, R. J., A Quantitative Statement of the Generator Theory of Single Nerve Cell Function, Ph.D. Thesis, Purdue University, 1967.

55. Hubel, D. H., and T. N. Wiesel, "Receptive Fields of Optic Nerve Fibers in the Spider Monkey," J. Physiol., Vol. 154, 1960, pp. 572-580.

56. Brown, K. T., and T. N. Wiesel, "Intraretinal Recordings with Micropipette Electrodes in the Intact Cat Eye," J. Physiol., Vol. 149, 1959, pp. 537-562.

57. Naka, K. I., and W. A. H. Rushton, "S-Potentials from Colour Units in the Retina of Fish (Cyprinidae)," J. Physiol., Vol. 185, 1966, pp. 536-555.

58. Naka, K. I., and W. A. H. Rushton, "S-Potentials from Luminosity Units in the Retina of Fish (Cyprinidae)," J. Physiol Vol. 185, 1966, pp. 587-599.

59. Bishop, G. M., "Natural History of the Nerve Impulse," Physiol. Rev., Vol. 36, 1956, pp. 376-399.

60. Moore, G. P., D. H. Perkel, and J. P. Segundo, "Statistical Analysis and Functional Interpretation of Neuronal Spike Data," Ann. Rev. Physiol , Vol. 28, 1966, pp. 493-522.

61 Lewis, E. R., and L. D. Harmon, "Neural Modeling," Physiol. Rev., Vol. 46, 1966, pp. 512-591.

62. Perkel, D. H., A Digital-Computer Model of Nerve-Cell Functioning, The RAND Corporation, RM-4132-NIH, 1964.

63. Lewis, E. R., "Neuroelectric Potentials Derived From an Extended Version of the Hodgkin-Huxley Model," J. Theoret. Biol., Vol. 10, 1965, pp. 125-128.

64. Segundo, J. P., D. H. Perkel, and G. P. Moore, Spike Probabilities in Neurones: Influence of Temporal Structure in the Train of Synaptic Events, The RAND Corporation, RM-4579-NIH, December 1965.

65. Gray, J., "Initiation of Impulses at Receptors," in Handbook of Physiology, Section 1, J. Field (ed.), 1959.

66. Eccles, J. C., The Physiology of Synapses, Academic Press, New York, 1964.

67. Brookhart, J. M., and K. Kubota, "Studies of the Integrative Function of the Motoneuron," in Brain Mechanisms; Prog. in Brain Res., Vol. I, G. Moruzzi, A. Fessard, and H. H. Jaspers (eds.), Elsevier, New York, 1963.

68. Rall, W., et al., "Dendritic Location of Synapses and Possible Mechanisms for the Monosynaptic EPSP in Motoneurons," J. Neurophysiol., Vol. 30, 1967, pp. 1169-1193.

69. Bullock, T. H., and C. A. Horridge, Structure and Function in the Nervous Systems of Invertebrates, Freeman Press, San Francisco, 1965.

70. Lewis, E. R., personal communication.

71. Eccles, J. C., The Physiology of Nerve Cells, Johns Hopkins University Press, Baltimore, 1957.

72. Thompson, R. F., and W. A. Spencer, "Habituation: A Model Phenomenon for the Study of Neuronal Substrates of Behavior," Psychol. Rev., Vol. 73, 1966, pp. 16-43.

73. Hughes, J. R., "Post-Tetanic Potentiation," Physiol. Rev., Vol. 38, 1958, pp. 91-113.

74. Bennett, M. V. L., et al., "Electrotonic Junctions Between Teleost Spinal Neurons: Electrophysiology and Ultrastructure," Science, Vol. 141, 1963, pp. 262-264.

75. Nelson, P. G., "Interaction Between Spinal Motoneurons of the Cat," J. Neurophysiol., Vol. 29, 1966, pp. 275-287.

76. Kandel, E. R., W. T. Frazier, and R. E. Coggeshall, "Opposite Synaptic Actions Mediated by Different Branches of an Identifiable Interneuron in Aplysia," Science, Vol. 155, 1967, pp. 346-349.

77. Ramon-Moliner, E., "An Attempt at Classifying Nerve Cells on the Basis of their Dendritic Patterns," J. Comp. Neurol., Vol. 119, 1962, pp. 211-227.

78. Henneman, E., G. Somjen, and D. O. Carpenter, "Functional Significance of Cell Size in Spinal Motoneurons," J. Neurophysiol., Vol. 28, 1965, pp. 560-581.

79. Granit, R., Receptors and Sensory Perception, Yale University Press, New Haven, 1955.

80. Magoun, H. W., The Waking Brain, Charles C. Thomas, Springfield, Illinois, 1963 (2nd ed.).

81. McIlwain, J. T., "Receptive Fields of Optic Tract Axons and Lateral Geniculate Cells. Peripheral Extent and Barbiturate Sensitivity," J. Neurophysiol., Vol. 27, 1964, pp. 1154-1173.

82. Ogawa, T., P. O. Bishop, and W. R. Levick, "Temporal Characteristics of Responses of Photic Stimulation by Single Ganglion Cells in the Unopened Eye of the Cat," J. Neurophysiol., Vol. 29, 1966, pp. 1-30.

83. Nelson, P. G., and K. Frank, "Extracellular Potential Fields of Single Spinal Motoneurones," J. Neurophysiol., Vol. 28, 1964, pp. 913-927.

84. Svaetichin, G., Acta, Physiol. Scand., Suppl. 134, Vol. 39, 1956, pp. 1-112.

85. Fröhlich, F. W., Grundzüge einer Lehre vom Licht- und Farbensinn, Fischen, Jena, 1921.

86. Granit, R., "Stimulus Intensity in Relation to Excitation and Pre- and Post-Excitatory Inhibition in Isolated Elements of Mammalian Retinae," J. Physiol., Vol. 103, 1944, pp. 103-118.

87. Broca, A., and D. Sulzen, "La Sensation Lumineuse en Fonction du Temps," J. Physiol. Path. Gén., Vol. 4, 1902, pp. 632-640.

88. Boring, E., A History of Experimental Psychology, Appleton-Century-Crofts, Inc. New York, 1957.

89. Stevens, S. S., "On the Psychophysical Law," Psychol. Rev., Vol. 64, 1957, pp. 153-181.

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10. ABSTRACT

A survey of the neurohistological, neuroelectrical, and neurophysiological data relevant to retinal organization. The data are derived from studies of the neural organization of the primate retina. Major current problems include mechanisms of adaptation, spontaneous activity, and efferent influence, details of interconnection patterns, and amacrine function. A theoretical framework for an initial consideration of retinal organization is developed and a model that attempts to account for the properties of graded potentials in the external plexiform layer is presented. The model specifies a hypothetical mechanism as the fundamental source of logarithmic intensity encoding.

11. KEY WORDS

Bioengineering
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